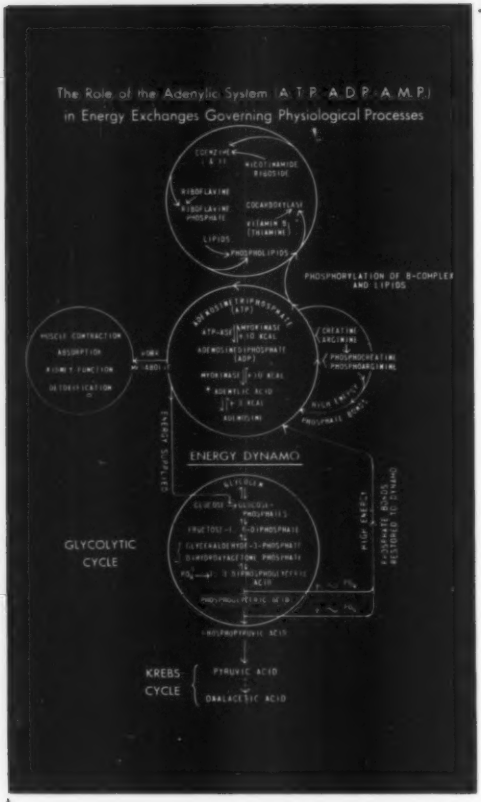
Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

AUGUST, 1956
Volume 6 — Number 8



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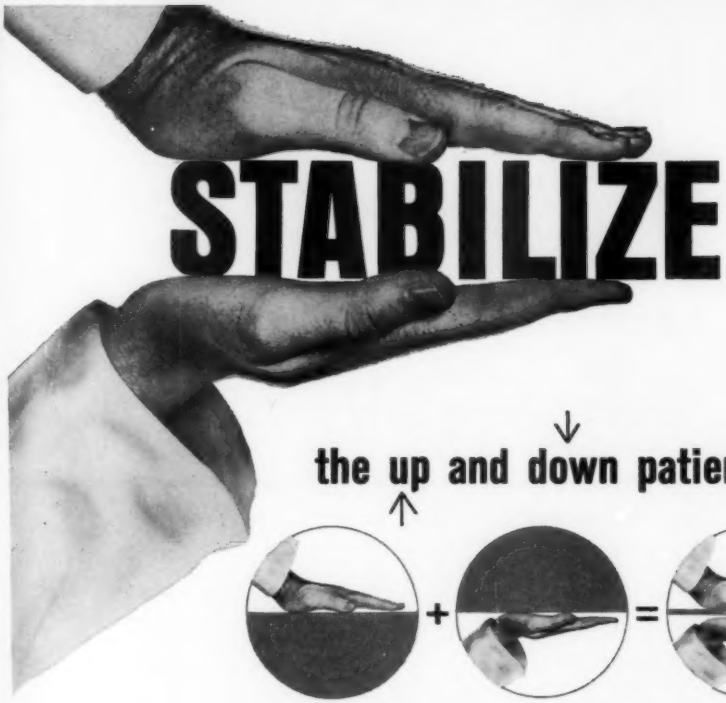

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1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M.C.: Personal communication.

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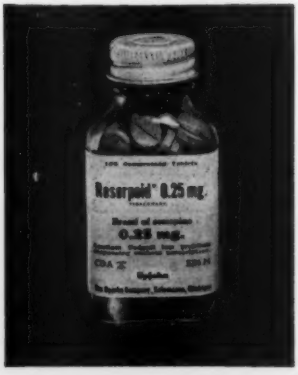

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1. Livingston, S., and Petersen, D.: New England J. Med. *254*:327 (Feb. 16) 1956.
2. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.
3. Berman, B. A.: Am. J. Psychiat. *112*:541 (Jan.) 1956.

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INFORMATION FOR *Authors*

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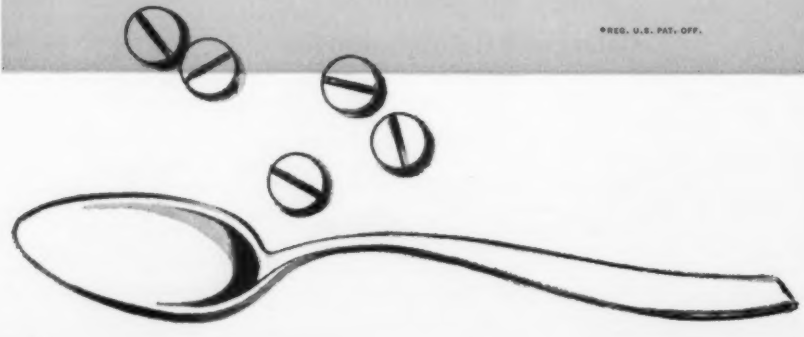

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1. Hollister, L. E., Krieger, G. E., Kringel, A., and Roberts, R. H.: Ann. New York Acad. Sc. *61*:92 (April 15) 1955. 2. Hoffman, J. L., and Konchegul, L.: Ann. New York Acad. Sc. *61*:144 (April 15) 1955. 3. Kline, N. S., and Stanley, A. M.: Ann. New York Acad. Sc. *61*:85 (April 15) 1955.

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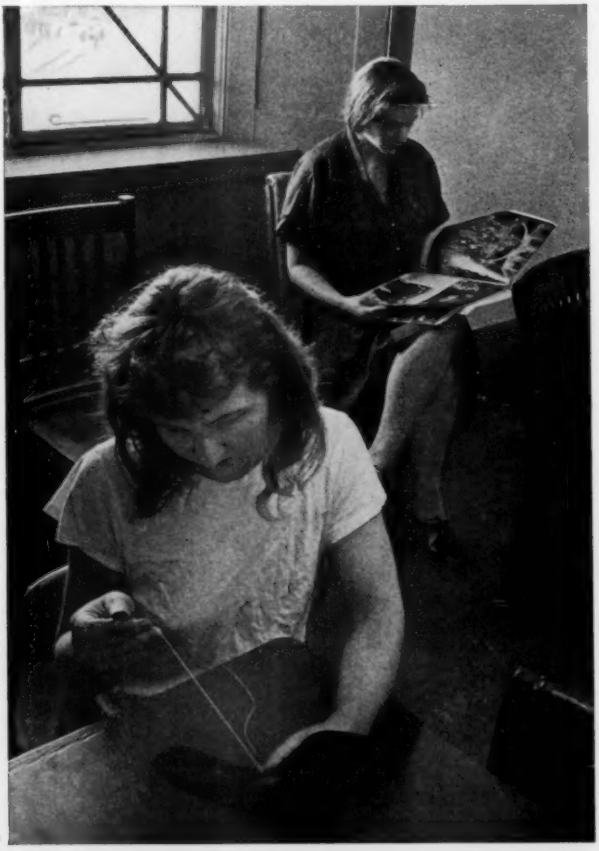

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Volume 6 Neurology Number 8

Spontaneous Occlusion of the Middle Cerebral Artery

Emanuel H. Feiring, M.D. and Bernard J. Sussman, M.D.

THE DIAGNOSIS of various forms of cerebrovascular disease has been greatly facilitated through the use of arteriography. In certain types of disease such as thrombosis of the internal carotid artery, an unequivocal diagnosis is virtually dependent upon the results of this method of study. In the course of a rather extensive experience with angiography, nine cases of demonstrable occlusion of the middle cerebral artery were encountered. On clinical grounds, the distinction between thrombosis of the middle cerebral artery and infarction resulting from a lesion affecting its ganglionic branches presents a difficult problem. Such a differentiation may, however, be established by means of arteriography. Admittedly this distinction may be of no more than academic interest in most cases, and, in fact, the authors do not recommend angiography as a routine diagnostic procedure in cases of cerebral thrombosis.

Analysis of our case material did, however, prove informative and will provide the subject matter of this presentation.

CASE MATERIAL

Case 1. Sudden occurrence of hemiplegia, hemisensory defect, and homonymous hemianopia in a 63 year old male. Suppression of electrical activity over affected hemisphere with bilateral slow wave activity. Development of increased intracranial pressure. Angiographic evidence of occlusion of middle cerebral artery. Death caused by postoperative infection.

A 63 year old, right-handed merchant entered the hospital on April 13, 1949 because of left-sided paralysis. This had occurred abruptly on the morning of the day of admission and was not associated with loss of consciousness. The previous day he had complained of severe headache over the right side. He was a known diabetic of 15 years' duration.

Physical examination: The patient was lethargic but oriented. He exhibited a left flaccid

From the neurosurgical service, Mount Sinai Hospital, and the department of neurosurgery, Albert Einstein College of Medicine, New York City.
Presented at a meeting of the New York Society of Neurosurgery, February 21, 1956.

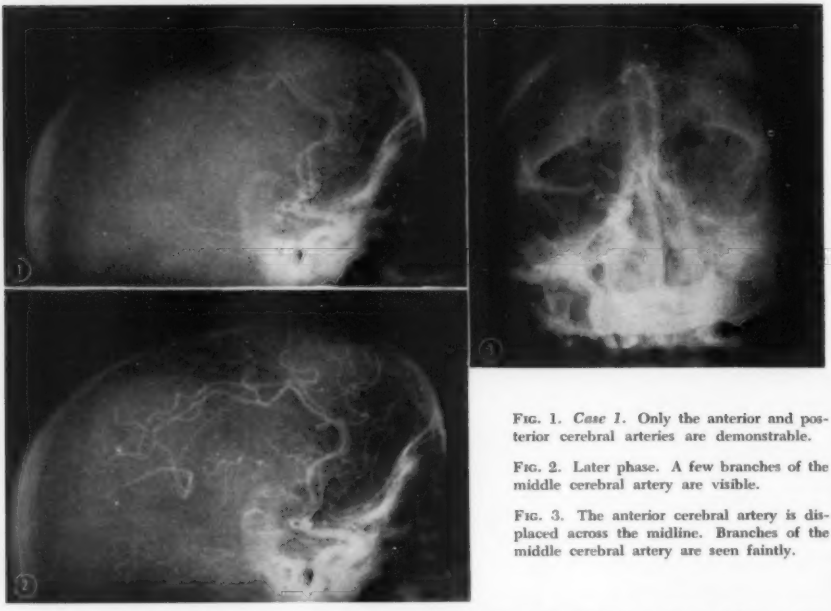


FIG. 1. *Case 1.* Only the anterior and posterior cerebral arteries are demonstrable.

FIG. 2. Later phase. A few branches of the middle cerebral artery are visible.

FIG. 3. The anterior cerebral artery is displaced across the midline. Branches of the middle cerebral artery are seen faintly.

hemiplegia, a left Babinski toe sign, and a tendency for the eyes to deviate toward the right. The tendon reflexes were all markedly depressed. The abdominal reflexes were not elicited on the left side. There was a left hemisensory defect affecting all modalities, as well as a left homonymous hemianopia demonstrable by confrontation. The fundi revealed narrowed retinal arteries. Blood pressure was 160/84.

Laboratory data: The blood count was normal. The urine contained a considerable amount of glucose (4+) and a trace of acetone. The fasting blood sugar was 213 mg. per cent and the nonprotein nitrogen 35 mg. per cent. Roentgenograms of the skull were normal. A chest film demonstrated poor aeration of the left lower lobe. Electroencephalography disclosed almost complete absence of alpha activity, together with suppression of voltage over the entire right hemisphere and a considerable amount of diffuse four to six per second serial and sporadic waves, of higher voltage on the left, except at the frontal and motor electrodes where the amplitude was about the same on the two sides.

Course: The patient's state of lethargy persisted. Diabetes was controlled by means of insulin and dietary measures. On the tenth hospital day a lumbar puncture was performed which revealed clear cerebrospinal fluid under normal pressure. Gradually the patient became more alert. Twenty-five days after admission, however, he was noted to be drowsy and papilledema was observed. Lumbar puncture disclosed clear cerebrospinal fluid, without any cells, under a pressure of 460 mm. water, containing 117 mg. per cent protein. On May 11, 1949 a right carotid arteriogram was performed. The anterior and posterior cerebral arteries were well visualized, the former appreciably displaced across the midline in the anteroposterior projection. Dye was seen relatively late in only a few smaller branches of the middle cerebral group of vessels, indicating an incomplete occlusion (figures 1 to 3). A right temporoparietal craniotomy was done the following day, exposing avascular cerebral tissue, obviously the site of an extensive infarct. Histologic study of a specimen of the tissue confirmed this impression. Following operation, the wound became infected with *B. pyocyaneus* and

Staphylococcus aureus. Antibiotic therapy was ineffectual and the patient expired on May 28, 1949.

Pathologic data: Postmortem examination was limited to the head. In addition to the evidence of infection, there was moderate atherosclerosis of the branches of the circle of Willis. The right middle cerebral artery was markedly sclerotic near its origin from the internal carotid artery and contained a recent thrombus; its lumen was greatly reduced (figure 4). Similar, though less marked, changes were observed in the left middle cerebral artery. Softening and necrosis involving the right cerebrum extended as far back as the inferior parietal and occipital lobes (figure 5). Small hemorrhages were present in the medial geniculate body, pulvinar, and thalamus on the same side.

Case 2. Hemiplegia and hemisensory syndrome of abrupt occurrence in a 37 year old female. Occlusion of middle cerebral artery diagnosed by angiography. Delta waves and diminished alpha activity on side of lesion.

A 37 year old, right-handed housewife was admitted to the hospital on June 25, 1949 because of paralysis of the limbs on the left side. On the evening of the day of admission, while dressing for dinner, she suddenly became dizzy and fell to the floor. She retained consciousness but immediately thereafter was unable to move the left upper or lower extremities. She vomited once. For many years she had been troubled with frequent headaches, and for a period of 24 hours prior to the advent of the paralysis she had experienced a particularly severe episode.

Physical examination: She was apathetic and tended to look toward the right. There was a flaccid left hemiplegia, impairment of sensation, and a questionable homonymous hemianopia on that side. The tendon reflexes were slightly more active and an extensor plantar response was demonstrable on the left. The abdominal reflexes were elicited only on the right side. Anosognosia was exhibited. Blood pressure was 114/70.

Laboratory data: The blood count was normal and the urinalysis negative. The fasting blood sugar was 83 mg. per cent and the nonprotein nitrogen 32 mg. per cent. Lumbar puncture revealed an intraspinal pressure of 160 mm. water; the cerebrospinal fluid was clear and contained no cells. The Wassermann reaction was negative. Roentgenograms of the chest and skull were normal. No changes indicative of myocardial disease were observed in the electrocardiogram. Electroencephalography disclosed less alpha activity and a considerable amount of slow wave activity of moderate voltage on the right side, maximal in the temporal and parietooccipital regions. In addition there were bisynchronous 2 to 4 per second bursts more marked and of higher amplitude on the right (figure 6). A right carotid arteriogram was performed which resulted in visualization of the anterior and posterior cerebral arteries exclusively (figure 7).

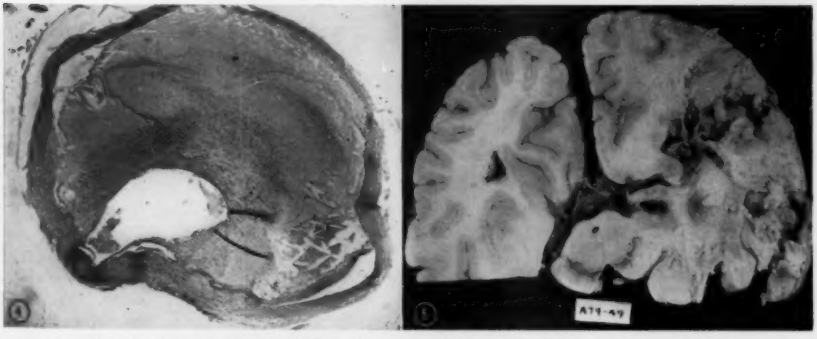
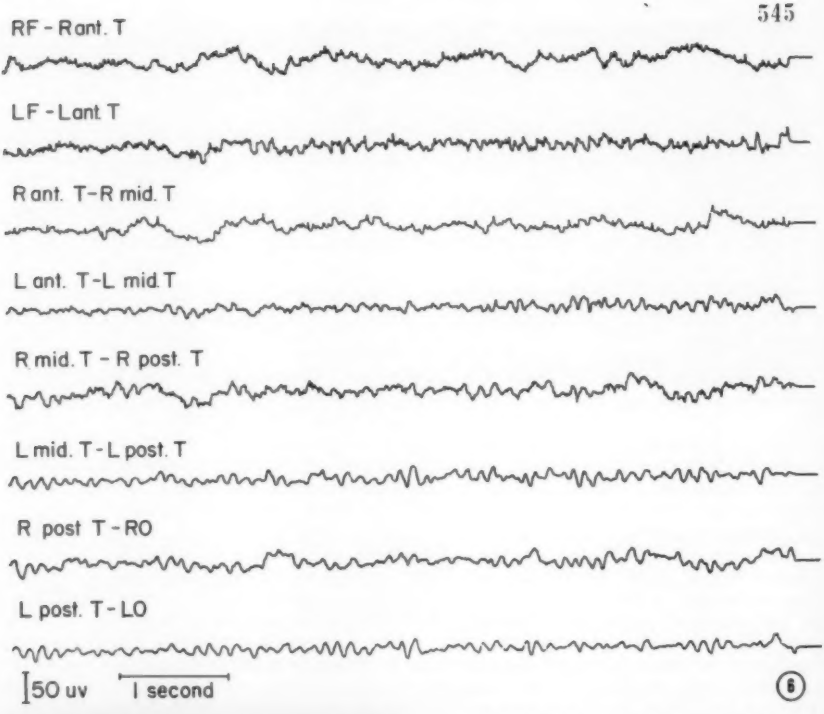


FIG. 4. *Case 1.* Low power magnification showing marked stenosis of right middle cerebral artery. It contained an antemortem thrombus.

FIG. 5. Extensive encephalomalacia of right cerebrum.



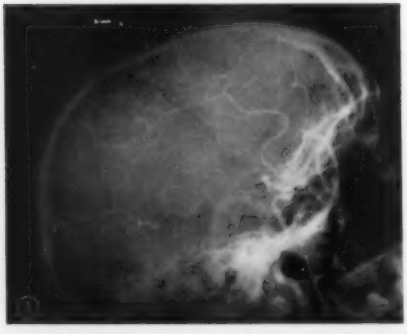


FIG. 6. *Case 2.* Slow-wave activity present on the right side.

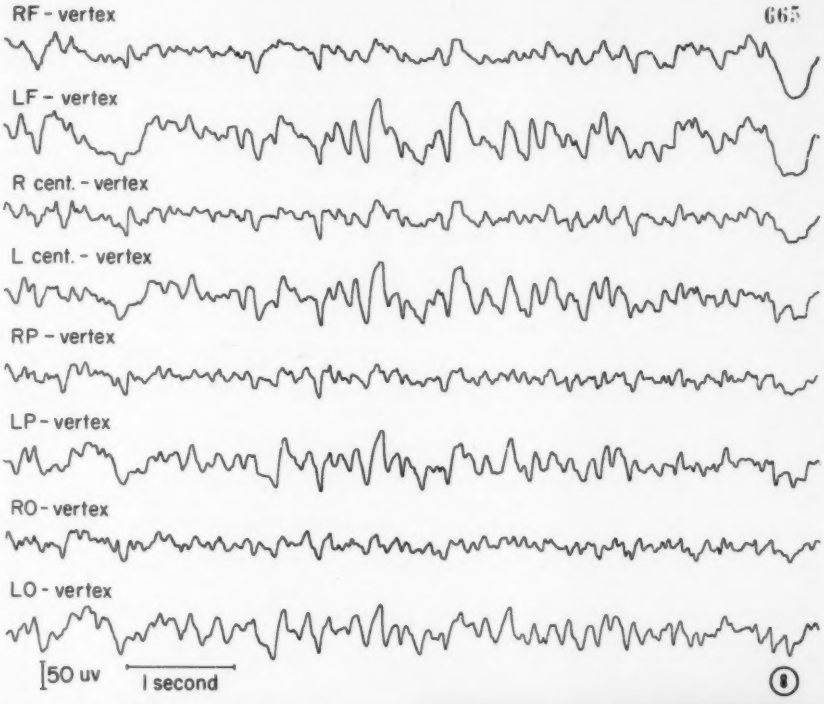
FIG. 7. Only the anterior and posterior cerebral arteries are visible.

Course: At the time of discharge four weeks later, the patient had regained some sensory perception and a very limited amount of power in the face and lower extremity.

Case 3. Abrupt onset of hemiplegia and aphasia in a 62 year old female. Occlusion of middle cerebral artery demonstrable angiographically two years later. Focal electroencephalographic abnormality. Lobotomy for pain. Postoperative death.

A 64 year old, right-handed housewife was first seen at the clinic on July 5, 1949 because of right-sided paralysis associated with pain. The hemiplegia together with loss of speech had developed abruptly two years previously and had persisted unchanged. Two months after the onset of paralysis, she began to have convulsions which started on the right side and became generalized. In addition, she developed severe pain on the affected side.

Physical examination: Speech was limited to unintelligible grunts, but judging from her responses she was able at least partially to comprehend what was said. She displayed a flac-



cid right hemiplegia with hypoactive tendon reflexes in the upper extremity, a hyperactive knee jerk, unsustained ankle clonus, and an extensor plantar response. Pinprick appreciation appeared to be defective in the involved upper limb. Stimulating the right side of the face or lower extremity with a pin evoked a markedly disagreeable response. Pathologic laughter and crying were often exhibited. The fundi revealed a moderate degree of arteriosclerosis. Blood pressure was 170/90. A loud, apical, systolic murmur was audible.

Laboratory data: The blood count was normal and urinalysis revealed no abnormalities. The fasting blood sugar was 98 mg. per cent and the urea nitrogen 12.7 mg. per cent. Roentgenograms of the chest and skull were essentially normal. The blood Wassermann reaction was negative. Electroencephalography revealed a large amount of one to six per second activity maximal at the left frontal, motor, and anterior and middle temporal electrodes, less prominent

FIG. 8. *Case 3.* Prominent high voltage slow-wave activity on the left side.

FIG. 9. The anterior and posterior cerebral arteries are well outlined. Dye is present in a few branches of the middle cerebral artery.

in the left posterior temporal region and minimal in the right anterior temporal and left parietal and occipital areas (figure 8). Injection of Diodrast into the left carotid artery resulted in excellent visualization of the anterior and posterior cerebral arteries. Only a few branches of the Sylvian group were demonstrable (figure 9).

Course: A prefrontal lobotomy performed on July 12, 1949 resulted in relief of the hyperpathia. A week following operation, however, the patient became febrile and subsequently semicomatose. Lumbar puncture disclosed an elevated pressure and a polymorphonuclear pleocytosis. The sugar content of the cerebrospinal fluid remained normal and no organism was cultured. Death occurred on the twelfth postoperative day. A necropsy was not performed.

Case 4. Hemiplegia and aphasia with loss of consciousness in a 48 year old female. Suppression of alpha together with slow-wave activity on side of lesion. Demonstration by angiography of occlusion of middle cerebral artery. No improvement.

A 48 year old, right-handed woman entered the hospital on October 31, 1949 because of right-sided paralysis and inability to speak of two weeks' duration. These symptoms had developed abruptly four days after a hemorrhoidectomy and were associated at the onset with loss of consciousness. During the preceding five months she had experienced recurrent episodes of numbness involving the right half of the body, as well as headache, tinnitus, and vertigo.

Physical examination: She presented a global aphasia and a flaccid right hemiplegia. The tendon reflexes were more active and a Babinski toe sign was demonstrable on the involved side. The abdominal reflexes were absent and pinprick appreciation was diminished on the right. The eye tended to deviate toward the left. Examination of the fundi disclosed blurred disks, suggestive of early papilledema. Blood pressure measured 120/76.

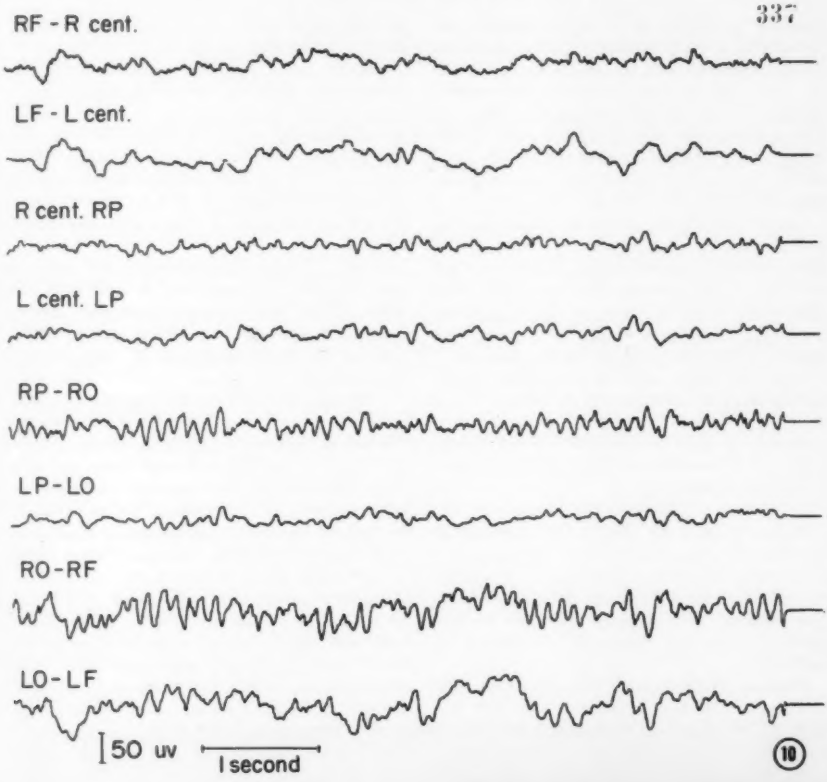
Laboratory data: The blood count was normal and the urine examination negative. The nonprotein nitrogen was 38 mg. per cent. A roentgenogram of the chest disclosed slight left ventricular enlargement; skull films were normal. The blood Wassermann reaction was negative. Lumbar puncture revealed clear, colorless cerebrospinal fluid under a pressure of 310 mm. water, containing no cells and 90 mg. per cent protein; the Wassermann and colloidal gold reactions were negative. Electroencephalography demonstrated marked suppression of alpha activity in the left parietal and occipital regions and, to a lesser extent, over the left temporal area; in addition, there was a moderate amount of low voltage, serial and sporadic, 2 to 4 per second activity in the left temporal region (figure 10). Injection of Diodrast into the left common carotid artery resulted in visualization of the ipsilateral anterior and posterior cerebral arteries only. A few ganglionic branches (anterior or middle cerebral artery origin?) were seen (figure 11).

Course: An anastomosis of the common carotid artery and jugular vein was performed on November 2, 1949 in the hope of improving the cerebral circulation. At the time of discharge from the hospital one month later, the patient's neurologic status was unchanged. According to information received in December 1954, the hemiplegia and aphasia were unimproved, but she was able to walk to a limited extent with the help of a cane and brace.

Case 5. Hemiplegia, hemisensory deficit, and aphasia in a 61 year old male with hypertension, peripheral vascular disease, and diabetes. Previous transient episodes. Slow-wave activity and depression of alpha in temporoparietooccipital region. Angiographic evidence of occlusion of middle cerebral artery.

A 61 year old, right-handed printer was admitted to the clinic on November 11, 1949 because of impairment of speech and right-sided paralysis. He was known to have diabetes, peripheral vascular disease, and hypertension for 15 years. In 1945 he developed a right hemiparesis which persisted for a week. In 1948 he suffered a recurrence of the paralysis for a period of several hours. On the day prior to admission he again suddenly developed right-sided paralysis and subsequently focal seizures involving the affected extremities. Loss of speech occurred on the day he entered the clinic. Consciousness was not affected.

Physical examination: The patient was lethargic and exhibited right hemiplegia. Speech was limited to the expression "all right." He was able to comply with simple commands only occasionally. The tendon reflexes were more active on the right and ankle clonus was demonstrable on that side. The abdominal reflexes were not elicited on the right. A right



hemisensory defect was evident and possibly also an homonymous hemianopia. Blood pressure was 190/94. Owing to the presence of a cataract, the right fundus could not be visualized; the left fundus appeared normal. There was a chronic ulcer over the left medial malleolus.

Laboratory data: The hemoglobin content of the blood was normal; there were 17,050 white cells per cu. mm., with a normal differential count. A moderate amount of acetone was present in the urine. The fasting blood sugar was 214 mg. per cent and the nonprotein nitrogen 40 mg. per cent. Roentgenograms of the skull were normal. A chest film revealed enlargement of the left ventricle. An electrocardiogram was not conclusively indicative of myocardial involvement. Electroencephalography

FIG. 10. *Case 4.* Marked suppression of alpha in the left parietooccipital region, together with slow-wave activity on that side.

FIG. 11. Lack of filling of the middle cerebral artery.

disclosed a depression of alpha activity, together with a small amount of low to moderate voltage, sporadic four to six per second activity in the left temporal, parietal, and occipital regions. An arteriogram performed on the left side outlined the vasculature of the anterior and posterior cerebral arteries exclusively; none of the branches of the middle cerebral group were visualized.

Course: During the period of hospitalization, several seizures involving the right side of the face and corresponding upper extremity were observed. These were readily controlled with phenobarbital. At the time of discharge from the hospital on November 22, 1949, speech was improved, but the paralysis was unchanged.

Case 6. Abrupt onset of hemiplegia, hemihypalgesia, and homonymous hemianopia in a 25 year old female. Diminished alpha together with diffuse delta activity on side of lesion. Occlusion of middle cerebral artery demonstrated by angiography.

A 25 year old, right-handed housewife entered the hospital on July 7, 1953 because of left-sided paralysis of four days' duration. The paralysis had developed precipitously following an episode of vomiting. Consciousness had not been affected. For a period of three months previously, she had frequently complained of headache.

Physical examination: She exhibited left hemiplegia, left hemihypalgesia, and left homonymous hemianopia demonstrable by confrontation. The tendon reflexes were hyperactive and the abdominal reflexes diminished on the affected side. Examination of the heart disclosed no abnormalities. Blood pressure was 112/80.

Laboratory data: The blood count was normal and the urine examination negative. Lumbar puncture demonstrated clear cerebrospinal fluid, with a protein content of 40 mg. per cent and no cells. Roentgenograms of the chest and skull were negative. An electrocardiogram revealed no abnormalities. Electroencephalography disclosed almost continuous sporadic and serial one to three per second waves of moderate voltage diffusely over the right hemisphere; alpha activity was diminished on that side (figure 12). Diodrast injected into the right common carotid artery resulted in visualization of only the anterior cerebral artery (figure 13). An anteroposterior projection revealed the middle cerebral artery to be occluded just distal to its origin from the internal carotid artery (figure 14).

Course: Some slight improvement, especially in the lower extremity, was evident at the time of discharge from the hospital one month later. At examination in March 1954, the left side was still considerably weaker. The fasting blood sugar was 112 mg. per cent and the nonprotein nitrogen 26 mg. per cent at this time. At present she is able to walk a little with the aid of a brace.

Case 7. Onset of hemiplegia and aphasia over a period of several days in a 64 year old male. Focal electroencephalographic abnormality in temporal region. Occlusion of middle cerebral artery demonstrated by angiography. Improvement.

A 64 year old, right-handed machine operator suddenly experienced difficulty in expressing himself on September 18, 1955. Three or four days later his right hand became weak, and two days thereafter he was completely unable to talk. His state of consciousness had not altered, nor had he vomited or complained of headache. Hypertension had been diagnosed some eight or nine years previously.

Physical examination: He was unable to speak and only partially able to comprehend what was said to him. A right facial paralysis, flaccid paralysis of the right upper extremity, and weakness of the right lower limb were present. A Babinski toe sign was demonstrable on the right side and the abdominal reflexes on that side could not be elicited. Sensation was probably diminished over the right half of the body. The visual fields could not be tested accurately. Blood pressure measured 210/110.

Laboratory data: The blood count was normal and the urine examination negative. The blood urea nitrogen was 19 mg. per cent and the fasting blood sugar 86 mg. per cent. Lumbar puncture revealed clear, colorless cerebrospinal fluid under a pressure of 130 mm. water, containing no cells and 32 mg. per cent protein. The blood and cerebrospinal fluid Wassermann reactions were negative. Roentgenograms of the skull disclosed no abnormalities. A chest film showed an elongated and tortuous aorta. Electroencephalography revealed almost continuous two to five per second activity in the left temporal region, most marked anteriorly; a small amount of slow-wave activity was also recorded from the left frontal region (figure 15). A left carotid arteriogram failed to dem-

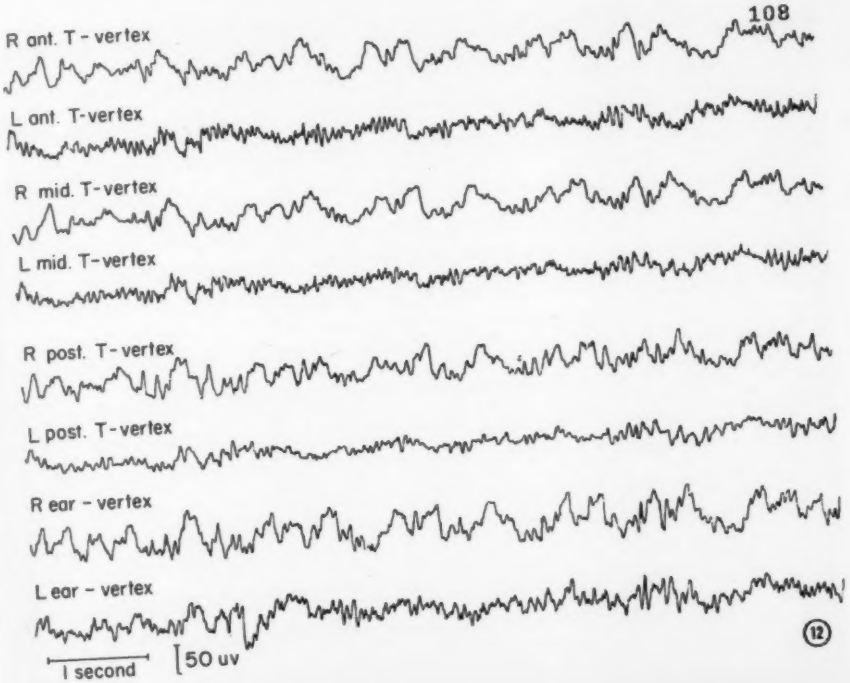


FIG. 12. *Case 6.* Diffuse slow-wave activity over right hemisphere.
FIG. 13. No filling whatsoever of the middle cerebral artery.
FIG. 14. Middle cerebral artery occluded just distal to its origin.

onstrate the middle cerebral artery in the "arterial" phase (figure 16); in the later phases of the arteriogram, dye was visualized in some vessels corresponding to the distribution of the middle cerebral artery, in all probability due to retrograde blood flow through anastomotic channels (figure 17). An anteroposterior projection disclosed occlusion of the middle cerebral artery just beyond the bifurcation of the internal carotid artery (figures 18 and 19).

Course: During his hospital stay the patient improved considerably. At the time of discharge on October 18, 1955, he was able to walk unaided and to speak to a limited degree. The weakness of the right side of the face and of the right upper extremity persisted.

Case 8. Sudden onset of hemiplegia and aphasia in a 42 year old male. Diminished alpha and considerable delta activity on side of lesion. Angiographic evidence of occlusion of middle cerebral artery. Improvement.

A 42 year old, right-handed male subway employee suddenly lost his speech and became paralyzed on the right side early on the morning of November 21, 1955. Consciousness remained unaffected. No history of previous neurologic symptoms or of cardiovascular disease was elicited.

Physical examination: The patient exhibited flaccid right hemiplegia and aphasia involving both receptive and expressive speech, the latter to a more marked degree. He was able to comprehend to a limited extent what was said. There was no appreciable alteration in the tendon reflexes, but the abdominal and cremasteric responses were absent on the right side. The plantar reflex was neither distinctly flexor nor extensor on either side. Pain was perceived less acutely over the right half of the body, and, by confrontation, there appeared to be a right homonymous hemianopia. Examination of the heart revealed no abnormalities. Blood pres-

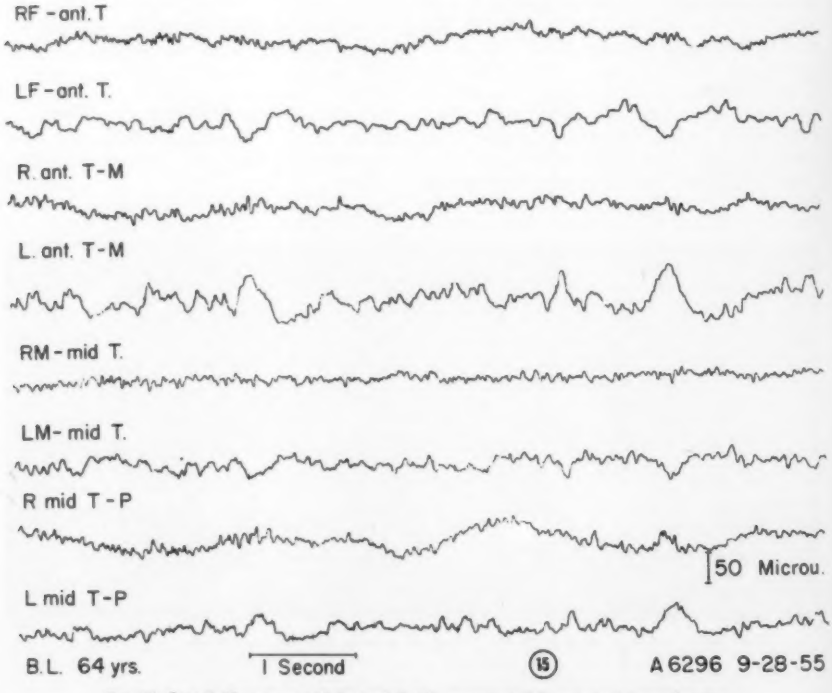


FIG. 15. *Case 7.* Slow-wave activity on left side, accentuated in anterior temporal region.

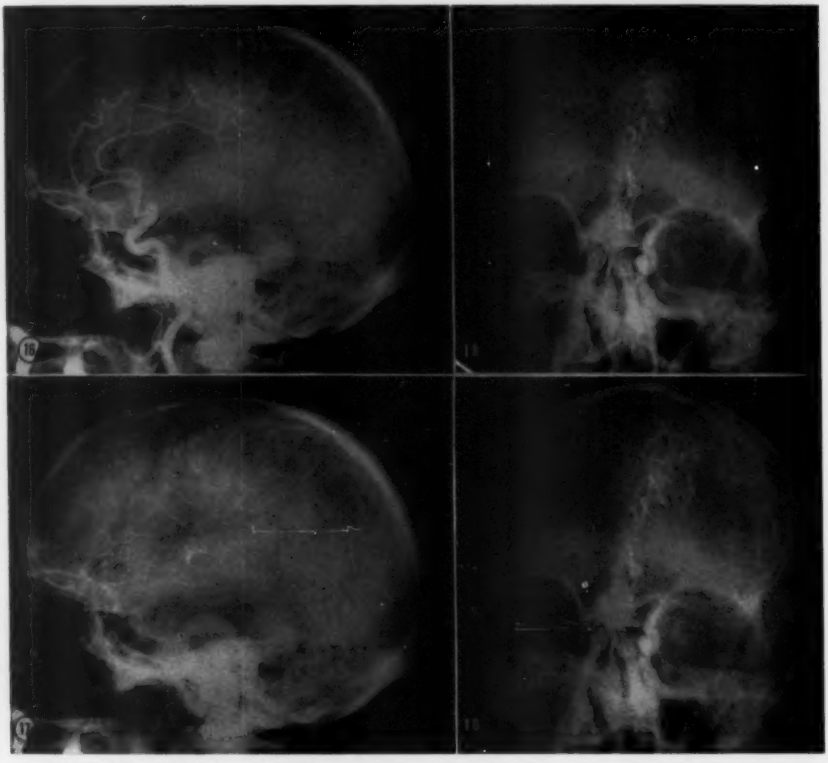


FIG. 16. *Case 7.* Middle cerebral artery not seen.
FIG. 17. Later phase. Blood vessels in the distribution of the middle cerebral artery are now visible.
FIG. 18. Middle cerebral artery occluded just beyond bifurcation of internal carotid.
FIG. 19. Later phase, showing evidence of anastomotic circulation.

sure measured 120/70.

Laboratory data: The blood count was normal and the urine examination negative. The blood urea nitrogen was 16 mg. per cent and the fasting blood sugar 97 mg. per cent. Roentgenograms of the skull and chest disclosed no abnormal features. Lumbar puncture revealed clear, colorless cerebrospinal fluid under a pressure of 75 mm. water, containing no cells and 49 mg. per cent protein. The blood and spinal fluid Wassermann reactions were negative. Electroencephalography demonstrated less alpha activity in the left temporoparietooccipital region, together with a large amount of delta activity with frequencies as low as one per second in the same distribution, maximal in the temporal area (figure 20). Injection of Diodrast into the left common carotid artery failed to outline the middle cerebral artery (figures 21 and 22); in the later phases of the angiogram, dye was seen in some vessels of the Sylvian system, evidence of a collateral circulation (figures 23 and 24). Not even the origin of the middle cerebral artery was demonstrable in the anteroposterior projection.

Course: The patient has shown considerable improvement in speech and has regained a moderate amount of strength in the right lower extremity.

Case 9. Focal manifestations of subacute on-

set due to occlusion of middle cerebral artery in a 60 year old male with cerebral arteriosclerosis. Angiographic demonstration of lesion. Progressively downhill course.

A 60 year old, right-handed window cleaner entered the hospital on September 30, 1955 because of weakness of the left upper extremity. About a year previously he had become aware of clumsiness of the right hand. He had been hospitalized a month earlier owing to unsteadiness of gait and transient weakness on the right side. At that time, in addition to mild right hemiparesis, it was noted that his speech was slow, that he blinked infrequently, and that his arm swing was diminished. Lumbar puncture disclosed clear cerebrospinal fluid under a pressure of 160 mm. water, containing no cells and 78 mg. per cent protein. Electroencephalography revealed no abnormality; a pneumoencephalogram showed a moderate degree of ventricular dilatation. Diabetes was diagnosed (fasting blood sugar 200 mg. per cent) and appropriate therapy instituted.

Six days prior to admission, he suddenly became unable to speak for a few minutes. Subsequently his left arm felt numb and weak and he noted difficulty with vision on the left side. On the day before his entry into the hospital, speech again became impaired and he was unable to swallow.

Physical examination: The patient was alert, but agitated and unable to speak. He complied with requests only occasionally. His head and eyes were deviated toward the right and he manifested paralysis of the left upper extremity and weakness of the left side of the face and

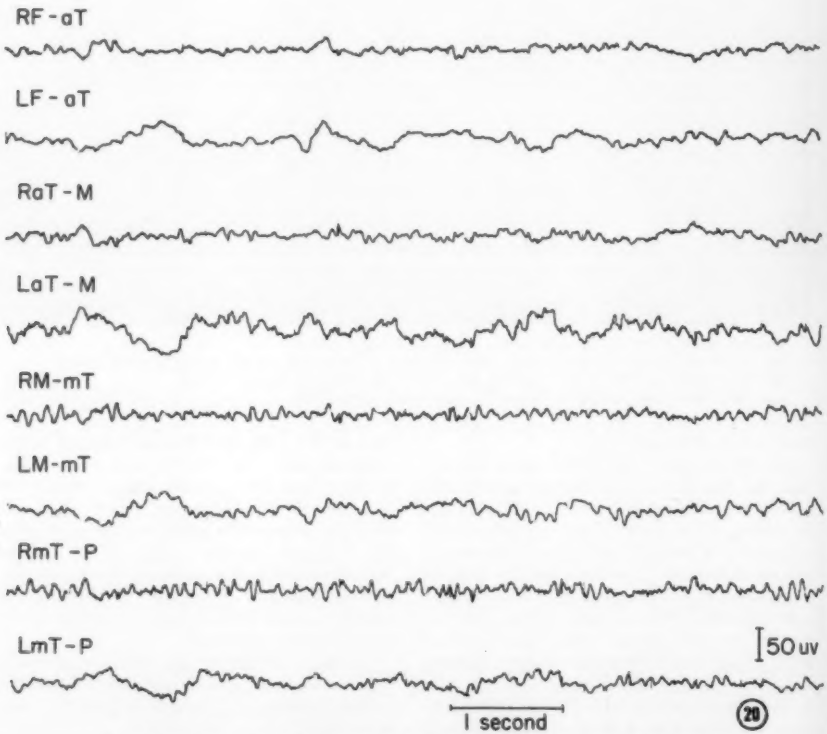


FIG. 20. *Case 8.* Delta activity with diminished alpha in left temporoparietal region.

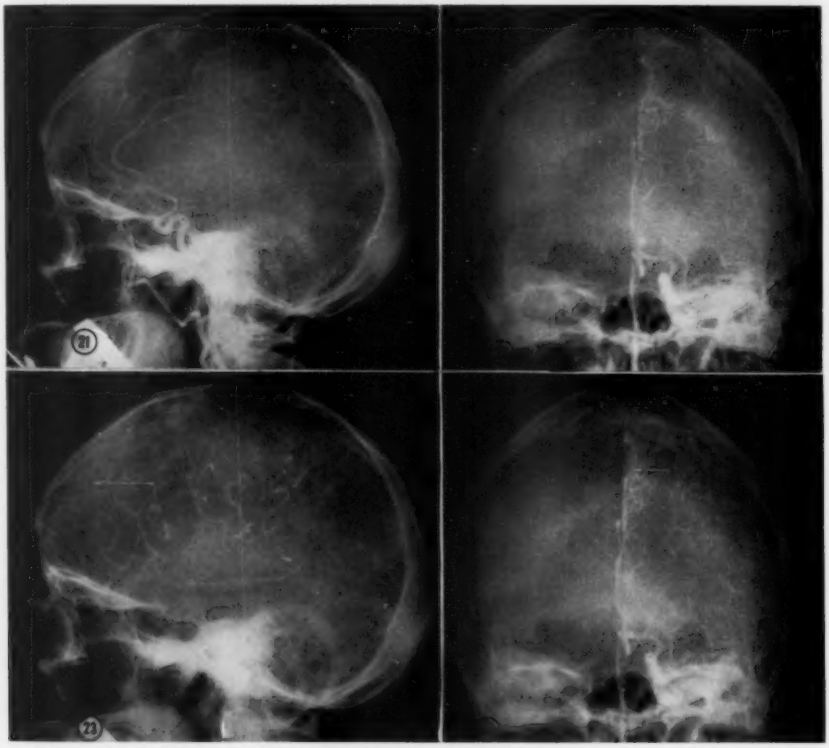


FIG. 21. *Case 8.* Failure of middle cerebral artery to be visualized.
FIG. 22. Similar phase as figure 21.
FIG. 23. Later phase revealing dye within branches of middle cerebral artery due to retrograde flow.
FIG. 24. Same phase as figure 23. Compare with figure 22.

lower limb. Rigidity was evident in the extremities on the right side. The gag reflex was absent. The tendon reflexes were very brisk bilaterally, despite which the plantar responses were flexor. There was a demonstrable left homonymous hemianopia and a suspicious hemisensory deficit. Blood pressure measured 200/120.

Laboratory data: The blood count was normal. Urinalysis showed a trace of acetone. The blood urea nitrogen was 12 mg. per cent and the fasting blood sugar 101 mg. per cent. Roentgenograms of the skull and chest revealed no abnormalities. The cerebrospinal fluid protein content was 34 mg. per cent. The blood and spinal fluid serologic reactions were negative. A right carotid arteriogram failed to demonstrate the trunk of the middle cerebral artery or its major branches in the initial films, both in the lateral and anteroposterior projections; only some ganglionic vessels were visualized. Dye was observed in a few small branches of the Sylvian group in films representing a later phase following the injection of Diodrast.

Course: The patient became increasingly lethargic and expired on October 9, 1955. Postmortem examination was not performed.

COMMENT

Although the ages of the patients at the time of onset of clinical symptoms

varied between 25 and 64 years, five of the nine were in the seventh decade of life. There was no sex preponderance. Three patients had diabetes, one had peripheral vascular disease, and four had hypertension. In all cases symptoms developed abruptly; progression of the neurologic deficit over a period of one or more days occurred in three cases. A history of previous transient episodes was elicited in one instance. Two patients complained of headache shortly before the vascular insult; two others had experienced headache for a longer period of time.

Loss of consciousness occurred in only one case. All patients exhibited hemiplegia, usually complete, though occasionally the lower extremity was less severely involved. Speech was invariably affected whenever the dominant hemisphere was the site of the lesion. A hemisensory defect was unequivocally present in seven cases; however, the likelihood is that sensation was impaired in all nine cases. An homonymous hemianopia was demonstrable in four patients and suspected in two; in the remaining three cases information bearing on this point was either lacking or inconclusive. Deviation of the eyes toward the side of the lesion was observed in four of the patients examined shortly after the onset of symptoms. In most cases in which a lumbar puncture was performed, the pressure and protein content of the cerebrospinal fluid were normal; in one case in which a pressure of 310 mm. water was recorded, the fluid contained 90 mg. per cent protein. One patient developed increased intracranial pressure under observation. Focal seizures developed in two cases. Hyperpathia involving the paralyzed side became a prominent feature in one patient.

Electroencephalographic data were available in eight cases. Suppression of voltage and almost complete absence of alpha activity over the affected hemisphere, together with diffuse bilateral slow-wave activity, generally of higher amplitude on the uninvolved side, were observed in one instance. In the remaining seven cases the electroencephalographic pattern was characterized by the occurrence of delta activity on the side of the lesion, maximal generally in the temporal region and usually combined with a diminution in amplitude and amount of alpha activity on the same side.

The diagnosis was established in all cases on the basis of the angiographic findings. In only one instance was the lesion verified anatomically. The angiographic feature common to all but one case was a failure of the trunk of the middle cerebral artery and its major branches to be visualized during the initial phase following an injection of Diodrast; a few branches of the Sylvian group were seen during this phase of the angiographic study in one case and in a later phase in an additional two cases; in all three cases the middle cerebral artery presumably was only partially occluded. Blood vessels in the distribution of the middle cerebral artery were visualized in films representing a later phase following the injection of the contrast medium in two cases, probably as a result of retrograde flow through anastomotic channels. In five cases in which anteroposterior as well as lateral views were available, occlusion of the middle cerebral artery was observed to occur at or slightly beyond its origin from the internal carotid artery.

A moderate degree of improvement occurred in two cases observed for a

relatively short time after the ictus; very little, if any, change was manifest, however, in four patients followed for a period of two years or longer.

DISCUSSION

The clinical manifestations in this series of cases of occlusion of the middle cerebral artery differ in no way from the observations already recorded in the literature.[1,2] Contralateral hemiplegia, hemisensory loss, homonymous hemianopia, and aphasia in the event the dominant hemisphere is affected, constitute the clinical picture. The occurrence of increased intracranial pressure in two cases, with overt manifestations in one, is worthy of comment. Intracranial hypertension resulting from cerebral thrombosis is uncommon and cerebrospinal fluid pressures above 300 mm. of water are rare.[3] The edema associated with a massive cerebral infarct may, however, be sufficiently pronounced to raise the intracranial pressure appreciably and even mimic a space-occupying lesion. Ventricular displacement suggestive of brain tumor was observed by King[4] in a patient with a thrombosis of the internal carotid artery extending into the anterior and middle cerebral arteries. Papilledema was reported in two of the 107 cases of thrombosis of the internal carotid artery collected by Johnson and Walker.[5] A significant displacement of the pineal body from the midline was described by Strully and co-workers[6] in a case of thrombosis of the internal carotid artery in the neck. Papilledema was present in one of 14 cases of complete occlusion of the middle cerebral artery reviewed by Davison, Goodhart, and Needles.[1]

The electroencephalographic findings observed in our material are noteworthy. In seven of the eight cases in which such data were available, delta activity, usually most pronounced in the temporal region together with a decrease in the amount and amplitude of alpha activity from the side of the lesion, was recorded. According to Strauss and Greenstein,[7] in about 70 per cent of cases of cerebrovascular disease no delta activity is demonstrable in the electroencephalogram. Schwab[8] stated that "in vascular lesions of the brain such as cerebral thrombosis or subarachnoid hemorrhage, 80 per cent of patients have normal electroencephalographic records taken four or five days after the episode . . . Directly after the onset of a cerebrovascular accident, the electroencephalogram may show mild focal disturbance over the area involved. In a few days this usually clears up, even if no return of motor function occurs." Cohn and his associates[9] found that prominent focal slow-wave activity occurred in patients with cerebrovascular disease only when the lesions were superficially located. In the monograph edited by Hill and Parr,[10] it is indicated that "local cerebral thromboses are usually detectable for a short period afterward and, if extensive enough, leave a low amplitude delta wave focus." The distinction in the electroencephalographic pattern between superficial and deep lesions is also emphasized by Roseman, Schmidt, and Foltz.[11] These authors stated that "in lesions at or near the electroencephalographically accessible surface, the electrical picture is that of delta activity corresponding to the site of the lesion plus associated physiological alteration (for example, vasospasm) . . . With a small lesion the electrencephalographic focus is small and sharp and may be limited to the vicinity of one or two electrodes. In a large lesion (for

example, thrombosis of an entire major vessel, such as the middle cerebral artery) the delta focus will be correspondingly greater. These foci may persist up to three or four months, depending on the extent of the lesion and the underlying pathology. In cases where there is much associated vasospasm, the bulk of the focus will disappear within three to five days. In instances with appreciable edema, there will be an increasing focus for three to ten days followed by a rapid resolution in the next three to five days. . . . In deep lesions of the brain, for example, internal capsule and brainstem, there is usually very little, if any, delta activity in evidence. The only notable findings are the amplitude asymmetries."

With regard to the observed electroencephalographic findings in thrombosis of the middle cerebral artery, Epstein, Lennox, and Noto,[12] in an experimental study in dogs, observed changes that varied with the size of the lesion, the time element, the technic of recording, and the state of consciousness. The most pronounced degree of abnormality occurred in animals with massive lesions and appeared as a flattening of electrical activity most evident in the frontal and temporal leads. After several weeks slow waves of high voltage replaced the flat record.

In a report on the electroencephalographic findings in various types of intracerebral vascular accidents, Abbott and Bautista[13] described "flattened voltages over the cortical distribution of the occluded vessel with suppression of activity, notably in the 8 to 13 per second range including occipital alpha activity on the affected side without conspicuous or unequivocal slow waves" in three cases of occlusion of the middle cerebral artery. Electroencephalography revealed a focus in the frontotemporal area of a patient with a thrombosis of the Sylvian vessels, observed by Wechsler and Gross.[14] Occlusion of the middle cerebral artery near its origin occurred in one of the cases included in a paper on thrombosis of the internal carotid system by Elvidge and Werner;[15] electroencephalography in this instance revealed slow waves over the affected hemisphere, together with alpha asymmetry. Based on a study of 14 cases of verified thrombosis of major cerebral arteries, Jones and Bagchi[16] concluded that it was possible to consistently lateralize and usually localize the pathologic area by means of electroencephalography. This series lists four instances of thrombosis of the middle cerebral artery, one of 12 months' and another of 18 months' duration prior to electroencephalography; in these cases slow-wave activity was usually evident in the midtemporal, anterior temporal, lateral premotor, lower motor, and lateral parietal areas, with the anterior and midtemporal regions being most involved. The electroencephalographic findings in eight cases of occlusion of the Sylvian trunk were described by Paillas and co-workers[17] in their monograph on thrombosis of the internal carotid artery and its branches. Delta activity in the temporoparietal region associated with a diminution in amplitude of alpha activity was found in two cases, polyrhythmic "pseudo-tumor" waves in the temporo-rolandic area in three, and delta activity with temporal spikes in two cases. The records of the remaining two patients revealed bilateral theta waves. The electrical pattern changed very slowly in those cases that were followed.

It has been indicated in a previous communication[18] that focal electroen-

cephalographic abnormalities are observed much more frequently in thrombosis of the internal carotid artery than in the other varieties of cerebrovascular occlusive disease. Judging from our experience and information gathered from the literature, it would appear that this conclusion applies equally to cases in which the middle cerebral artery is occluded at or near its origin.

In two of our cases, blood vessels were seen in the distribution of the middle cerebral artery in a "postarterial" phase, presumably due to retrograde blood flow through anastomotic channels. Since serial angiography in our earlier experience was limited to three films, it is possible that an anastomotic circulation might otherwise have been demonstrable in a greater proportion of cases. The existence of anastomoses between cortical arteries has been known for some time, and their potentiality as a means of providing a collateral blood supply was recently emphasized by Vander Eecken and Adams.[19] They described a case in which the trunk of the middle cerebral artery was occluded, despite which all the branches of the vessel were patent; the extent of infarction attributable to cortical ischemia was relatively small, presumably due to an effective collateral circulation derived from the anterior and posterior cerebral arteries. It is indicated that arteriosclerosis affecting such anastomotic vessels could seriously interfere with this function. Attention is also drawn to the fact that the basal ganglia and brainstem are especially vulnerable to vascular disease, the source of their blood supply being nonanastomosing penetrating arteries. Thus, in the case of occlusion of the middle cerebral artery mentioned above, in which the degree of cortical infarction was relatively slight, extensive cavitation was observed in the deeper structures supplied by the lenticulostriate branches.

Based on a study of the collateral circulation in cases of occlusion of a major cerebral artery, Rosegay and Welch[20] concluded "that in some cases at least, the anterior and posterior cerebral arteries are capable of taking over the cortical vascular territory of the middle cerebral, and that the paralysis that follows occlusion of the middle cerebral at its origin is then capsular and not cortical in origin." Angiographic evidence of an arterial anastomotic circulation in cases of occlusion of the middle cerebral artery is available in a number of additional publications.[21–23]

SUMMARY

The frequent occurrence of a focal electroencephalographic abnormality in association with occlusion of the trunk of the middle cerebral artery is sufficiently noteworthy to warrant its inclusion as an additional feature of the syndrome. It is further suggested that occlusion of a major artery is the responsible factor whenever increased intracranial pressure develops in conjunction with cerebrovascular disease. Probably in such cases the anastomotic circulation is deficient so that extensive infarction ensues. Lastly, additional evidence of a collateral blood supply following thrombosis of the middle cerebral artery has been presented.

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■ Now we must point out a capital distinction which relates to the extent (in length) of the alteration in the posterior columns. If the alteration is very little extended, it allows reflex actions to take place; but, if, for instance, it extends to the whole of the lumbar swelling, it prevents these actions, and as walking, standing, etc., cannot be perfected without them, it follows that there is a degree of apparent paralysis of voluntary movements. If the alteration extends to the whole length of the posterior columns, the loss of reflex action in the muscles of the limbs renders their voluntary movements much less powerful. It is not so in cases in which the alteration of the posterior columns occupies only a small part of their length; reflex action persisting, voluntary movements are hardly diminished.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Irreversibility of Motor Function Following Bilateral Simultaneous Cortical Lesions

A. M. Lassek, Ph.D., M.D. and Sara L. Emery, M.A.

ONE OF THE STANDARDS which might be valuable to know in the cerebral motor system of primates is what constitutes the safety and nonsafety factors in respect to traumatic lesions and paralysis. One question is: Just how much and what cortical tissue needs to be removed at one time to produce a physiologic state of paralytic prostration from which there is no restitution of function? Another, at the other extreme, is: How much can be extirpated with impunity so that recovery under laboratory conditions can occur? This problem is associated with vital and probably obscure brain mechanisms about which little is known but which, nevertheless, are of great practical significance. The views regarding recovery of motor function following injury to the central nervous system have remained in the theoretical stage since the beginning of modern neurology, suggesting the complexity of these problems. The aim of this project is to ascertain the answers to what cortical ablations of the cerebrum, their location and extent, are necessary to produce irreversibility of motor function on the one hand and reversibility on the other.

Most of the extirpation experiments which have been performed in the central region of the cerebral cortex of primates have been unilateral. In general, the opinion prevails that excision of one motor cortex (area 4 of Brodmann) in the monkey produces only a temporary motor deficit. Return to normal has been reported following such an operation within a month's time.[1] Denny-Brown[2] also stated that recovery is remarkable in degree and rapidity. According to him, removal of area 4 merely causes a depression of motor function rather than a true paralysis. He designates this as "pyramidal shock."

Bilateral, simultaneously placed lesions of the Rolandic areas of primates have been rare. Mettler[3] ablated area 4 on both sides at one time in a single monkey, and found no complete prostration. The animal was able to sit, stand, walk, and climb, but it died on the twenty-first postoperative day, indicating an adverse internal reaction from the operation.

Bucy and Fulton[4] stated that, when areas 4 and 6 are removed from both hemispheres in an animal (primate), it is totally incapacitated and reverts to the thalamic reflex level. Most of the surgical cortical ablations performed by them to determine this physiologic mo-

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This work aided by a grant from United Cerebral Palsy.

tor deficit were done in conjunction with other operations, such as labyrinthectomy; in addition, they were spaced. We have not been able to find any complete protocols on animals who had bilateral and simultaneous removal of the motor projection area.

The results of the investigations that have been done suggest, therefore, that the primate brain has a considerable safety factor in respect to loss of the region immediately in front of the central sulcus. However, attention has not been specifically focused on this question, and the number of animals used has been negligible. Scientifically, we may not have the answer as to what the qualitative and quantitative characteristics may be.

MATERIAL AND METHODS

Because unilateral ablations do not produce maximal motor deficits, the bilateral approach was used entirely. Simultaneous extirpations were made in 40 monkeys (37 Macacus mulatta, 3 macacus irus) in the central region of the cerebral cortex by the suction technic. No attempt was made to delimit exact areal boundaries. The motor cortex (area 4 of Brodmann) and underlying fibers were basically involved in all operations; in some, invasions were made into the premotor and postcentral regions.

For the experiments designed to study irreversibility of motor function, the following surgical operations were performed: 15 more or less complete extirpations of area 4, seven removals of the precentral gyrus, and eight in which the postcentral convolution was included.

Ten monkeys were utilized for the reversible study. In these, incomplete lesions were made in the motor cortex, consisting of strip areas of variable lengths and widths paralleling the central sulcus.

Although the attempt was made to obtain animals of uniform age, size, species, and physical condition, this was not possible. The animals differed in all of these categories, the smallest averaging about four pounds in weight and the largest, 11 pounds. Their physical status also varied from fair to excellent, although all were shipped as well-conditioned and fit subjects.

Postoperatively, each monkey was observed daily and given complete neurologic examinations at spaced intervals. A prostrate animal showing irreversible motor deficits was judged as such when it was unable to move itself for as long as it survived: to sit, stand, climb, feed itself, or show any detectable signs of restitution of function. The degree of spasticity or flaccidity, although noted, was not stressed. In the reversible group were placed those animals which exhibited gradually increasing recovery to the extent that they could make postural adjustments and perform phasic movements. In this classification were included some whose internal resistance seemed to be affected as the result of the operation, so that they might undergo deterioration suddenly to a degree that they succumbed or were sacrificed.

After autopsy the placement of the cerebral lesions was determined both grossly and by means of histologic sections stained with cresyl-violet. The latter was done only in those animals who survived for eight or more days. The degenerative response of the pyramidal tract to the extirpation performed was also determined by studies of sections made through the brainstem and spinal cord stained by both the protargol and silver-nitrate methods.

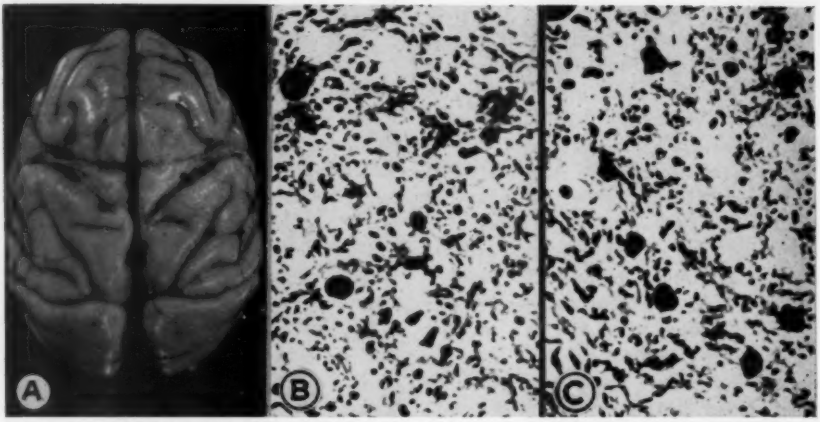

FIG. 1. *A*. Bilateral area 4 lesions in Rhesus monkey. *B* and *C* show preservation of mostly small fibers in the pyramids, 77 days postoperative. Largest black spots are over-stained glial nuclei. Protargol stain.

RESULTS

Motor prostration, characterized by irreversibility or nonrestitution of function, is the outstanding symptomatology produced by the bilateral and simultaneously placed lesions in the pre- and postrolandic regions of the cerebral cortex in monkeys. Area 4 of Brodmann, or the motor cortex, is the key and vital structure which is intimately linked with the deficit phenomenon. From the standpoint of this investigation, when it is removed entirely on both sides at one operation, the physiologic motor deficits are usually devastating. In 12 out of 15 monkeys (group 1), the picture simulated in some respects that of a thalamic reflex animal. They were immobilized, unable to sit, stand, walk, run, climb, or eat by themselves. Occasional, random pawing movements with the freed extremities while lying on their sides were the only motor signs shown and then by only a few. Of the three animals which retained some motor function, two could sit up and one could climb in a weak fashion; they tired easily. The average survival time postoperatively for the group was five days, with variations from two to eight days. Five of the group were sacrificed because of poor condition, and ten died spontaneously.

In the 15 animals (group 2) where the extirpations were extended from area 4 rostrally to involve the premotor or posteriorly to include the postcentral region, the motor deficits were much the same. Complete prostration occurred in 13. Of the two remaining, one could sit in a frog-like fashion; the other sat and walked in a crude and uncertain manner, with extremities maximally abducted and abdomen scraping the floor. The average survival time for this series was 12 days, with a range from two to 39 days.

In group 3 (10 monkeys) where partial or incomplete ablations were made in area 4, much less over-all motor deficits with obvious signs of return of function were the rule. All but one possessed the strength to sit up, walk, and even climb immediately after the operation; from that stage on, they exhibited resti-

tution of function to the degree where they could perform purposeful phasic movements, being able to pick up kernels of corn by opposing thumbs and forefingers. Some of the animals who had incomplete lesions of area 4 showed favorable signs of recovery for a while and then suddenly deteriorated rapidly to the stage of death. This course of events developed in five animals, whose average postoperative survival time was 23 days. The remaining five were sacrificed while they were in good physical condition at a mean of 64 days. The only defects detected at this time were somewhat slower movements and a tendency to tire more easily.

The gross and histologic studies of the extent of the lesions show that, in general, the intended areas were removed satisfactorily. Variations in the relations of the arcuate, the central, and the intraparietal sulci to each other were noted, which accounted for some differences in the quantity of cortical tissue removed in the animals in each of the three groups. The depth varied also; in one case the lesion extended almost to the basal ganglia. In none of the monkeys which survived more than seven days did the pyramidal tract below show a complete loss of fibers. This is true whether area 4, the entire precentral gyrus, or area 4 plus the postcentral convolution were involved. The majority, especially the small fibers, many of the medium-sized, and even a few of the largest fibers always remained intact.

DISCUSSION

The over-all picture which is presented by bilateral and simultaneously placed lesions of the motor cortex is greatly different from that following either unilateral or spaced extirpations on both sides; they are much more severe and devastating. As mentioned previously, only temporary and relatively minor motor deficits are reported from unilateral ablation of area 4.[1,2] Ades and Raab[1] also found that when a second operation is performed on the opposite motor area of the monkey three to four months after the first, the animal fails to show any but the most meager signs of pyramidal dysfunction.

By contrast, bilateral and simultaneous removal of area 4 alone tends to produce a physiologic status akin to a thalamic reflex animal, with complete prostration the rule. The ability to initiate the remaining motor system into any sort of purposeful movement is lost on a permanent basis, even though the animals may try hard to arise to a sitting or standing position. The brain mechanisms, whatever they may be, do not respond in the same manner when this tissue is injured bilaterally at one time. The paralysis, depression, or diaschisis produced is such that the initiating, directing, and controlling neurologic factors necessary to positively influence the lower motor neurons is so disoriented that return to normal is remote. Denny-Brown[2] believed that the synaptic connections at the anterior horn cell level may be so affected in pyramidal lesions that their resistance is increased. If that is true, it may occur in such exaggerated form that descending neural impulses from the cerebrum cannot break through.

In the adult monkey there is a safety region (area 4) in the total brain which cannot be destroyed without producing a suppression of all somatic motor activity. This harmonizes with the fact that this part of the cerebral cortex is

the most sensitive as proved on several counts. It responds most easily to electrical stimulation, it has the largest cells (Betz), and it is associated with the known origin of the pyramidal tract. The acute loss of these well-known cellular elements and the fibers beneath may explain the syndrome we obtained.

Restitution of function is possible to a surprising extent when as much as one-half to three-quarters of the posterior portion of area 4 is removed on both sides at one time. It appears to be almost as rapid in degree as that which follows unilateral removal. Within two months after operation the animals are able to move around the cage or on the floor in a coordinated and well-timed fashion. The performance of skilled movements, characterized in part by the ability to oppose thumb and forefinger, returns in these animals. This indicates that the same forces responsible for restitution are at work as in unilateral area 4 extirpations.

It is possible that the condition of the animals may be of some significance in the final results we have obtained. Those in a perfect physical state and in their natural habitat might possibly withstand more successfully the bilateral operations we have performed upon area 4, but probably not much more. In the laboratory specimens used, bilateral area 4 is the crucial region.

There are considerations in these experiments which may go beyond an effect upon somatic motor functions extending into the autonomic nervous system. The resistance of the animals and their vital functions seem to be impaired so that their postoperative survival time is markedly shortened. We have not investigated this phase of the problem.

What has been found to be true in the rhesus monkey would undoubtedly be the case in man and probably in a much more exaggerated form since motor function is more encephalized.

CONCLUSIONS

In the laboratory monkey there is a motor safety factor relating to the amount and quantity of cortical tissue which can be lost acutely at one time with impunity to the animal. The critical region is bilateral area 4 down to the corpus striatum. Irreversibility of motor function from a condition of complete prostration is the rule when traumatic lesions are made involving this division of the cerebral cortex. The depression is such that the ability to initiate and control purposeful movement is permanently affected. Animals show reversibility or restitution of motor function to a status approaching normal when as much as three-quarters of the posterior part of area 4 is extirpated bilaterally and simultaneously. The recovery in these cases is relatively rapid over a two-month postoperative period. Such operations also appear to lower the resistance of some animals, possibly through an effect on visceral and vital nerve elements below. The dynamics of the monkey brain appear to be totally disoriented by sudden loss of the Betz cell area on both sides.

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Anticonvulsant Action of Diamox in Children

J. Gordon Millichap, M.D.

ALTHOUGH the antiepileptic effect of acetazoleamide (Diamox) has been established by clinical trial,[1,2] reports concerning the types of seizures benefited have varied and the mechanism of the anticonvulsant action has remained obscure. It is generally postulated that the drug influences seizure activity by means of the metabolic acidosis consequent to the inhibition of renal carbonic anhydrase, and its anticonvulsant effect has been compared with that of the ketogenic diet. In support of this theory, it has been stated that Diamox is particularly effective in the control of seizures of the petit mal type, which are known to be influenced by acid-base changes, and that the patients most likely to benefit are those who show a marked alteration in the electroencephalogram or develop clinical seizures in response to hyperventilation and respiratory alkalosis.[3]

In a recent study of the mechanism of action of Diamox, however, Millichap, Woodbury, and Goodman[4] have demonstrated in animals that the anticonvulsant effect is not abolished by nephrectomy and is therefore independent of the action on the kidney and the resultant metabolic acidosis. A direct relation between the anticonvulsant effect and the inhibition of brain carbonic anhydrase was shown by comparing the activity of Diamox with that of sulfanilamide, a much less potent inhibitor. Diamox was approximately twice as potent as sulfanilamide, both as an anticonvulsant and as an inhibitor of brain carbonic anhydrase, and the maximum degree of brain enzyme inhibition corresponded with the time of peak anticonvulsant effect of each drug.

The prevention of major as well as minor seizures might, therefore, be expected from Diamox therapy. To obtain clinical support for the laboratory findings, a controlled trial of the drug has been carried out in children with seizures of the type not specifically responsive to acid-base changes. The results of this study indicate that seizures other than petit mal may be controlled by Diamox and that the anticonvulsant effect is not restricted to seizures which are influenced by hyperventilation and alkalosis.

CLINICAL DATA

Fourteen children, nine girls and five boys, were included in the study; their ages ranged from six months to 11 years, with an average of four and one-half

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years. In all cases the seizures were of organic etiology and were secondary to brain injury or a congenital developmental disorder. A family history of seizures was obtained only in two patients. Mental defect was present in 12 patients and of these, eight were severely retarded both mentally and physically. A diagnosis of cerebral palsy was made in seven, and hyperkinetic behavior occurred in five.

The seizures were classified according to clinical type, electroencephalographic pattern, anatomic localization, and response to previous therapy. Except for one child who had myoclonic jerks alone, major seizures occurred in all patients. In seven patients, two of whom had psychomotor attacks, the seizures were focal in type, and in six they were generalized. The generalized myoclonic jerks, which occurred in six patients and were associated with major seizures in five, were of the type sometimes classed as "massive myoclonic" or "minor motor seizures." They consist of a sudden generalized spasmodic movement, with flexion of the neck, abduction and flexion of the upper extremities, and, in infants and young children, flexion of the lower extremities. These attacks are of short duration and occur frequently, sometimes 50 to 100 times each day.

The electroencephalogram was abnormal in all patients, and the dysrhythmia was diffuse and without definite localization. Seizure discharges occurred in ten patients, some asymmetry in eight, and a tendency to bilateral synchrony and possible subcortical involvement in three. Hyperventilation failed to alter the electroencephalogram or to induce seizures in five patients who were able to perform the test; in all patients the seizures were of the type generally not influenced by acid-base changes.

The previous response to conventional anticonvulsant drugs had been poor, or their use was limited by toxic effects, such as sedation, ataxia, hyperirritability, nausea, and vomiting. Diphenylhydantoin (Dilantin) and primidone (Mysoline) had proved the most effective agents in the control of both myoclonic and major seizures.

CONTROLLED EXPERIMENT

Patients with frequent seizures and under reasonably constant surveillance were chosen for the study. The reliability of the parents' observations was assessed, and a printed form was provided on which to record the number of seizures each day and any unusual symptoms or signs. The children were seen at intervals of two weeks for clinical examination and for blood and urine investigations. On each occasion the white and red blood cell counts, the platelet count, and the hemoglobin value were determined, and the urine was examined microscopically and for protein and reducing substances. Because of the danger of status epilepticus on withdrawal of anticonvulsant medication, the existing medication, phenobarbital, Dilantin, or Mysoline, was continued in the same dosage during the trial period.

Diamox tablets and a control placebo were prescribed alternately to successive patients, and the double-blind technic was employed. Initially, 375 mg. was given daily in three divided doses, and according to the response, the dose was increased at intervals of two or four weeks up to a maximum of 750 mg. daily. The average daily dose range by body weight was 18 to 36 mg./kg. After an adequate trial of the new therapy, which varied in duration according to

TABLE 1
SEIZURE INCIDENCE DURING CONTROL PERIOD AND DIAMOX THERAPY

Patient Number	Age (years)	Sex	Control: Seizure Incidence weekly Range	Control: Seizure Incidence weekly Average	Diamox: Seizure Incidence weekly Minimal	Diamox: Seizure Incidence weekly Final* Average	Duration of Treatment (weeks)	Additional Medication
1.	5	F	3-5	4	0	0	26	Phenobarbital
2.	1½	F	2-20	11	0	0	8	Phenobarbital
			35-56	45	0	30		
3.	3	M	7-10	8	0	0	10	Phenobarbital
			50-150	100	25	39		
4.	3½	M	14-22	18	0	2	9	Mebaral
			148-193	170	5	157		
5.	4	F	36-48	42	1	5	16	None
6.	½	F	35-54	46	5	18	5	Phenobarbital Dilantin
7.	11	F	37-58	44	18	23	8	Phenobarbital Mysoline
8.	7	M	1-3	2	0	1	7	Phenobarbital Gemonil
9.	9	F	7-9	8	1	4	12	Mebaral Dilantin
10.	5	M	105-140	122	60	60	5	Phenobarbital
11.	10	F	1-3	2	1	1	18	Mebaral Dilantin
12.	1	F	160-230	195	105	125	6	Phenobarbital Dilantin
13.	2	M	35-48	41	30	34	6	Phenobarbital Mysoline
14.	4	F	5-9	7	4	7	10	None

*Average based on seizure incidence during last 4 weeks of therapy.

the response, the alternate preparation was substituted. Since seizures were frequent and severe in some patients while taking the placebo tablets, the control period in such cases was of necessity short.

In five patients the anticonvulsant effect of Diamox was also compared with that of Dilantin, the drug currently accepted as the treatment of choice in the seizures under study. The drug suspensions prepared for use in this controlled investigation were indistinguishable in appearance, taste, and odor. During treatment with each drug, increments in dosage were added until the optimally effective or largest tolerated dose was employed. Except for two patients in whom the withdrawal of Dilantin was necessary owing to the occurrence of toxic effects, the duration of treatment with each preparation was approximately the same.

RESULTS

In table 1 the average weekly incidence of seizures in the control period is compared with that during Diamox therapy. Figure 1 shows the maximal and final percentage reduction of seizures; the maximal effect of Diamox was assessed by comparing the average weekly number of seizures in the control period with the lowest weekly incidence recorded during treatment, and the final effect was based on a comparison with the average weekly incidence during the last four weeks of the trial.

An anticonvulsant effect was demonstrated in all patients; both major and myoclonic seizures were reduced in frequency at some time during the course

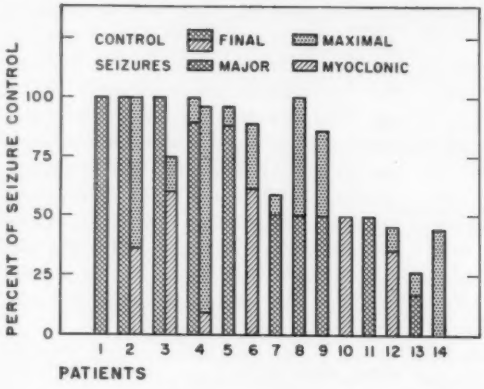

FIG. 1. Effect of Diamox on major and myoclonic seizures.

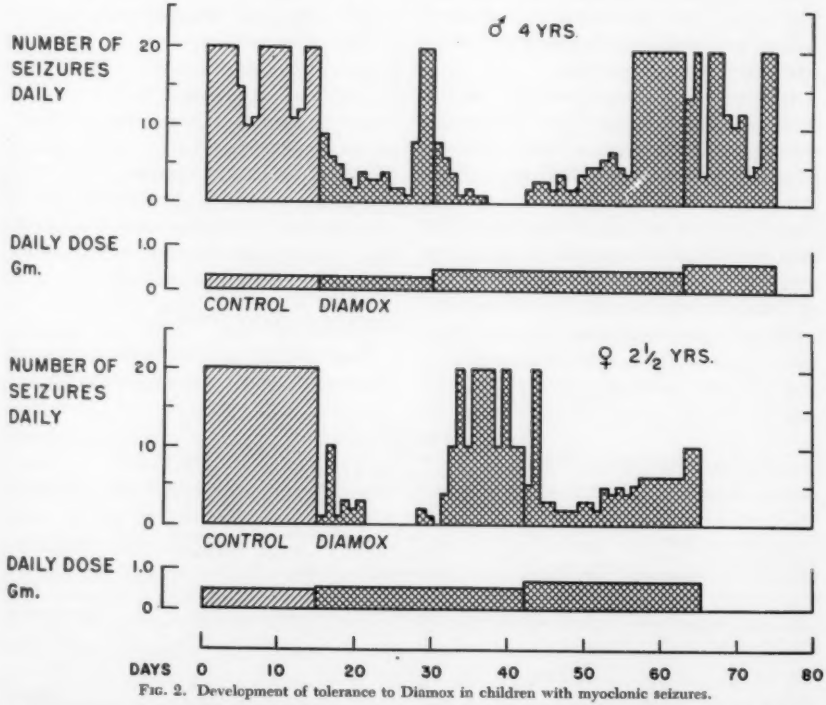

FIG. 2. Development of tolerance to Diamox in children with myoclonic seizures.

of treatment. The optimal dose interval was not investigated, but the drug was effective when given in two, three, or four divided doses daily. In eight of the total of 14 patients, the maximal reduction in seizures was more than 75

per cent, and in five a similar degree of control was obtained at the end of the trial period. The control of major seizures was superior to that of the myoclonic type.

Development of tolerance to Diamox in two patients is shown in figure 2. In seven patients who became refractory to the drug, treatment was discontinued at the completion of the trial. An exacerbation of seizures occurred in three patients during the initial introduction of Diamox and in five others on its withdrawal and substitution by Dilantin or placebo. In five incompletely controlled patients seizures were less severe and postictal depression and irritability were diminished.

In table 2 the incidence of seizures is shown, and in figure 3 the percentage seizure control is compared during treatment with Diamox and Dilantin. Five patients had major seizures and two of these also had myoclonic seizures. The degree of control was about the same with each drug; in two patients the use of Dilantin was limited by its toxicity.

Psychologic evaluation showed that the attention span was increased and hyperkinetic behavior was diminished in three patients. The electroencephalogram was repeated in three patients following chronic treatment with Diamox; the dysrhythmia was unchanged in one patient and in two a moderate improvement was seen. In two adult patients not included in the trial, who showed a continuous bilaterally synchronous three per second, spike-and-wave discharge in the electroencephalogram, Diamox, 250 mg. intravenously, had no immediate effect on the record and the petit mal status was not controlled.

TOXIC EFFECTS

Side effects of Diamox were reported in ten of 14 patients treated, and their frequency, as shown in parentheses, was as follows: anorexia (five), polyuria (five), nocturnal enuresis (four), drowsiness or lassitude (three), pallor (two), vomiting (one), and diarrhea (one). The symptoms were benign and, except for anorexia and lassitude, were not persistent. Laboratory studies of the blood and urine showed no abnormality.

ANTICONVULSANT POTENCY

The average anticonvulsant dose of Diamox in this study was 28 mg./kg.

TABLE 2

EFFECT OF DIAMOX AND DILANTIN ON THE INCIDENCE OF MAJOR AND MYOCLONIC SEIZURES

Patient Number	*Control Seizure Incidence weekly Average*	*Diamox*		*Dilantin*		*Additional Medication*
		*Seizure Incidence weekly Average**	*Percent Seizure Control*	*Seizure Incidence weekly Average**	*Percent Seizure Control*	
1.	42(2)	5(15)	88	3(16)	93	None
2.	8(2)	0(10)	100	3(9)	63	Phenobarbital
	100	39	61	45	55	
3.	41(3)	34(6)	17	45(6)	0	Phenobarbital Mysoline
4.	18(2)	2(9)	90	0(2)†	100	Mebaral
5.	11(5)	0(8)	100	0(2)†	100	Phenobarbital
	45	30	36	32	30	

Duration of treatment in weeks is indicated in parentheses.
*Average based on seizure incidence during last 4 weeks of therapy.
†Toxic effects necessitated withdrawal of Dilantin.

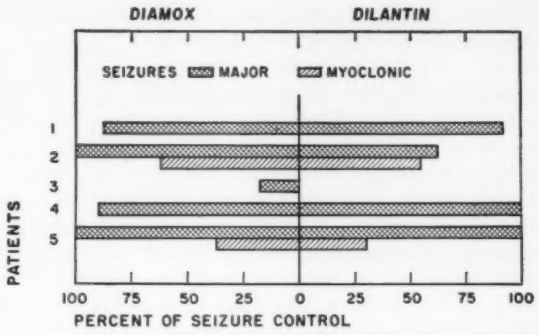

FIG. 3. Effect of Diamox compared with Dilantin on major and myoclonic seizures.

daily, which is relatively large when compared with the dose necessary to affect renal function; for example, Bergstrom and co-workers[1] have reported a metabolic acidosis with a dose of 8 mg./kg. daily in one patient with petit mal.

In laboratory investigations,[4] Diamox was found to be one hundred times more potent than sulfanilamide as an inhibitor of carbonic anhydrase in vitro; but, as an anticonvulsant and an inhibitor of the enzyme in the brain, it was only twice as potent. The brain concentration of Diamox was one-fiftieth that of sulfanilamide at the same dose levels, and its relatively weak anticonvulsant potency is, therefore, explained. Goldsworthy and co-workers[5] have noted a direct correlation between the acidic dissociation constants of sulfonamides and their rates of permeation into the brain of rats. A low pKa of Diamox is associated with the low brain concentration observed in animal studies, and the necessity for relatively large doses of Diamox in the treatment of seizures might be expected.

TOLERANCE

In the present clinical trial, tolerance to Diamox was exhibited in eight of 14 patients treated, and the practical value of the drug was thereby reduced. Woodbury and Rollins[6] first demonstrated the development of tolerance to Diamox in mice with experimental seizures; Millichap and co-workers,[7] in subsequent studies, have shown that ammonium chloride, though ineffective as an anticonvulsant when given alone, will potentiate and prolong the action of chronically administered Diamox. Ammonium chloride was given to three children as an additional medication in the present trial, but the onset of nausea and diarrhea precluded the continuation of the treatment and the evaluation of its clinical effects. In older children and adults who are able to tolerate ammonium chloride, a satisfactory response might be obtained.

A reduction in carbonic anhydrase activity is known to accompany a fall in pH, and the mechanism of the potentiating effect of ammonium chloride may be related to the acidosis it produces. Though the anticonvulsant activity of Diamox is independent of the effect on the kidney, the metabolic acidosis, as an additional component of its action, has not yet been excluded. In a study which was monitored by the aid of electroencephalograms, Bercel[8] suggested that diuretics facilitate the ad-

mittance of anticonvulsants to the brain and potentiate their effects by an increase in the blood-brain barrier permeability. However, in animals treated with ammonium chloride and Diamox, the brain concentration of the carbonic anhydrase inhibitor, when estimated directly, was not increased, and its potentiation by ammonium chloride could not be explained by an effect on the blood-brain barrier.

DISCUSSION

In this controlled study, the anticonvulsant action of Diamox was comparable to that of Dilantin, the drug currently accepted as the treatment of choice in the patients selected; major and generalized myoclonic seizures not specifically influenced by hyperventilation and respiratory alkalosis were controlled by the addition of Diamox to the existing medication. Therefore, seizures which are usually unresponsive to acid-base changes may be benefited. The anticonvulsant effect of Diamox is not restricted to the petit mal seizures which are exacerbated by alkalosis.

Repeated estimations of blood pH and total carbon dioxide were impracticable in this out-patient study of infants and young children; but, in one patient with petit mal admitted to this Institute, Wells observed that the seizure incidence during treatment with Diamox was unrelated to the changes in acid-base balance.[9] In a report by Cohen and Cobb[10] concerning the antiepileptic effect of the carbonic anhydrase inhibitor, sulfanilamide, there was no correlation between the number of seizures on a given day and the values for the chemical constituents of the blood. Also, patients whose seizures were controlled by sulfanilamide were not benefited when ammonium chloride was substituted.

Clinical studies, therefore, are in agreement with the laboratory findings. In animals the production of an acidosis or alkalosis has little or no effect on experimental convulsive seizures.[11] The anticonvulsant activity of Diamox, which is independent of its effect on the kidney and the resultant metabolic acidosis, is related directly to the inhibition of carbonic anhydrase in the brain.[4]

Carbonic anhydrase in the nervous system was first demonstrated by Ashby,[12] who considers that the enzyme plays a role in brain metabolism; it is thought to hasten the removal of carbon dioxide incident to the firing of neurons and thus to accelerate the return of nerve sensitivity. Carbon dioxide decreases the speed of nerve conduction and increases the electrical threshold, and its possible accumulation in the brain following Diamox therapy may be significant in the prevention of seizures. Indeed, both carbon dioxide and Diamox prevent maximal electroshock seizures in animals, and Woodbury and Rollins[6] have shown that the anticonvulsant effect of Diamox is potentiated by carbon dioxide.

The results of preliminary experiments in mice[4] suggest that changes in the brain electrolytes, as a result of the direct inhibition of brain carbonic anhydrase, must also be considered in a study of the intimate mechanism of the anticonvulsant action of Diamox. That the enzyme carbonic anhydrase has some function in the metabolism of the nervous system is suggested by the experimental studies described, and further investigation of the anticonvulsant action of carbonic anhydrase inhibitors may elucidate the seizure mechanism.

SUMMARY

The anticonvulsant effect of Diamox, a carbonic anhydrase inhibitor, has been demonstrated in children with seizures other than true petit mal and of the type not specifically influenced by hyperventilation and alkalosis.

Major and generalized myoclonic seizures of organic etiology and refractory to conventional antiepileptic compounds were controlled when Diamox was given as an additional medication, but in some patients its continued effectiveness was limited by the development of tolerance. Compared with Dilantin in five patients, the response to Diamox was remarkably similar. An exacerbation of seizures occurred occasionally when Diamox therapy was started, and more frequently on its withdrawal. In patients incompletely controlled, seizures were less severe and postictal depression and irritability were diminished. Of the side effects encountered, anorexia and lassitude were the most troublesome and persistent.

The clinical findings are compatible with recent laboratory observations that the anticonvulsant action of Diamox is directly related to the inhibition of brain carbonic anhydrase and is independent of the metabolic acidosis which results from inhibition of the enzyme in the kidney. Seizures of all types may be benefited and, if equally potent congeners of Diamox are developed which can reach higher concentrations in the brain, the anticonvulsant activity should be greater and the clinical value enhanced.

The laboratory investigations connected with this project were performed, in cooperation with Dr. Dixon M. Woodbury and Dr. Louis S. Goodman, at the department of pharmacology, University of Utah College of Medicine, Salt Lake City.

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Meralgia Paresthetica

Robert Wartenberg, M.D.

MERALGIA PARESTHETICA, also called Bernhardt-Roth's disease, is an affection of the lateral cutaneous nerve of the thigh. It is comparatively common, much more so than may be judged from the discussion of this entity in the literature and in textbooks. The affection usually takes a mild course or even remains unnoticed, and a doctor is rarely consulted. An unduly large proportion of physicians among the patients is best explained by the fact that a physician observes himself more carefully than does a layman and reports his observations to his fellow physician. The diagnosis is easy but still often missed since the disease is not well known.

To find the etiology of the disease, however, is difficult; it was a puzzle to the first observers[1,2] in 1895 and has remained so. A review of the literature shows that there is hardly any disease to which the human body can be heir that has not been claimed at one time or another as causing meralgia paresthetica. Yet, even now, experienced clinicians are often unable to find any definite cause of the disease. Doctors,[3,4] who were themselves patients and who studied their own condition, have often been puzzled as to what might have been the cause.

Neurologically, every point of the cerebrospinal axis from the periphery up to the thalamus has been assumed at one time or another to be the seat of the affection. The most popular theory is that meralgia paresthetica is a compression neuritis. Most authors, particularly neurosurgeons, assume that meralgia is "a purely mechanical condition."[5] This theory has found its way into the textbooks, most of which plainly state that the cause of meralgia paresthetica is compression of the nerve. Very often this tenet is emphatically and positively presented as if it had been definitely established. Although some writers qualify their statement, saying that meralgia paresthetica is "usually,"[6] "probably,"[7] or "presumably"[8] due to compression, some express the view in a way that leaves no doubt. One author[9] said: "For many years considered a mere neuralgia, the condition (meralgia paresthetica) is now known to be true compression neuritis . . ."

It is true that the lateral cutaneous nerve of the thigh is unfavorably located mechanically, and may easily be subject to compression, strangulation, or stretching at several points of its course. But traumatogenic cases can easily be recognized as such. In the vast majority

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of cases, however, trauma of any kind cannot be incriminated.

The mechanical theory does not cover the whole problem, and against an exclusive orthopedic or mechanical origin of meralgia paresthetica the following objections can be raised:

1) Meralgia occurs in middle age, and evolutionary changes must be blamed for mechanical irritation of the nerve. But nothing is known about these changes which cause such severe damage to the nerve. The orthopedic status of the patients is completely normal.

2) If evolutionary changes were the pathogenic factor, the disease should start always in middle age, but it may start at the age of five, or it may start also as late as in the sixth or seventh decade.

3) If the origin of meralgia were mechanical, that is, in the form of a slow acting compression, then we would expect the disease to be insidious in onset, slow in progress, and lead eventually to complete interruption of conduction of the nerve. This is not the case. The disease starts full-blown. The onset may be acute. The complete signs and symptoms appear suddenly and do not progress, but remain more or less the same, although there may be remissions and intermissions. There are mild, abortive, transient forms. Ecker and Woltman state: "When symptoms have lasted less than two years, the chances are two to one that they will disappear spontaneously within another two years."[10] The affection seldom leads to complete interruption in the conduction of the nerve. The sensory defect remains the same during the duration of the disease. All this does not occur in a compression neuritis.

4) The definitely established fact that meralgia often occurs in close relation to infections of many kinds speaks against a purely mechanical, orthopedic origin for the disease. In the first cases described by Bernhardt,[1] there was "most probably a connection of meralgia paresthetica with typhoid fever or lead poisoning." It has been estimated that infections account for 30 per cent of cases of meralgia paresthetica. Next to typhoid fever, the following infections most commonly have been mentioned as a source of meralgia paresthetica: syphilis, grippe, malaria, measles, rheumatism, yellow fever, scurvy, typhus fever, scarlatina, pneumonia, acute rheumatism, recurrent fever, cerebrospinal meningitis, tuberculosis, diabetes, follicular tonsillitis, mucomembranous colitis, gonorrhea, herpes, vaccination, injection of antitetanic serum, and carbon monoxide poisoning.

Often meralgia paresthetica is attributed to exposure to cold, as in "rheumatic" (infectious) facial paralysis. It is remarkable that a polyneuritis can start with a meralgia paresthetica, and upon recovery from polyneuritis the patient may have as a residuum only a meralgia which may be the last phase of the polyneuritis. Meralgia may be a stage of migrant sensory neuritis; that is, at one time during the disease the lateral cutaneous nerve of one side or both sides may be affected after and before other sensory nerves are involved.

5) Other sensory nerves may be involved at the same time. This is often overlooked by both the patient and the physician, since the clinical manifestations may be very mild. Herpes zoster or neuralgia of different locations may accompany, precede, or follow meralgia paresthetica. In a discussion of 17 cases

occurring after typhoid fever, it has been said: "Mild neuritic phenomena in areas of other nerves were observed in most cases: aching pain in legs and arms, tenderness of the brachial plexus to pressure, pain on stretching of the sciatic nerve, tenderness of the exit points of trigeminal nerves."[11] Meralgia paresthetica is often found in combination with affections of other cutaneous nerves of the thigh, with sciatica, and with motor neuritides of single nerves somewhere in the body.

6) Just as there is a constitutional disposition to polyneuritis, there is also such a disposition to meralgia paresthetica. The familial and hereditary occurrence point in this direction.

7) The histologic changes found in meralgia are nil or insignificant. Were this disease mechanically or orthopedically conditioned, these changes would be more pronounced.

All this speaks against a purely mechanical etiology of meralgia. However, the importance of a mechanical factor cannot be denied. It must only be assumed that this mechanical factor plays a subordinate role. The unfavorable location of the nerve is a predisposing factor for action of some other general pathologic agent. This chronic traumatization makes the nerve a place of least resistance where a generalized toxi-infectious process settles easily and first. Thus meralgia paresthetica is a local manifestation of a systemic infection.

Among the many toxi-infectious processes possible, a virus infection may play a role, but to what degree cannot be said. We can say with some certainty that an exclusive or dominant role cannot be assigned to the mechanical factor. Something else must be at work here – some general infection or perhaps virus infection.

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Epileptic Tendencies of the Normal Monkey

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RECURRENT EPILEPTIC SEIZURES in the monkey, produced by the application of aluminum hydroxide to the cerebral cortex, were first reported in 1942.[1] Since that time the method has proved useful in studying many physiologic mechanisms underlying excitation of the nervous system.[2–4] The development and march of epileptic signs in the monkey is now well known and follows an established pattern which is similar to that seen in man when epilepsy appears as a result of cortical injury. These cinical changes are paralleled by electroencephalographic changes in both man and monkey.

However, there has been some confusion and much discussion among laboratory workers because, although normal monkeys seldom, if ever, develop clinical seizures, a form of paroxysmal electroencephalographic pattern frequently appears in normal monkeys and is difficult to distinguish from the paroxysmal pattern of the animal made epileptic by cortical potentiation, either temporarily by Metrazol or permanently with aluminum hydroxide.[2]

In our laboratory, also, normal unoperated monkeys in the resting unanesthetized state have developed generalized paroxysmal patterns of a few seconds' to several minutes' duration which contain spike-like activity as well as the high-voltage slow and fast wave-forms which are also seen in the electroencephalograms of the epileptic animal. However, these paroxysmal patterns are never localized except that they are more apparent in frontal than in occipital regions. They are always bilateral in contrast to the spike potentials produced by aluminum hydroxide.[2]

In the present paper, the characteristics of their occurrence in 18 normal monkeys will be described and compared with the electroencephalographic patterns produced in these same monkeys by: 1) bilateral ablation of the frontal poles, and 2) application of aluminum hydroxide to the cerebral cortex.

METHOD

A group of 18 animals were normal immature rhesus monkeys which were being prepared for another investigation

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to be reported later. The findings are supplemented by casual observations of the electroencephalographic status of many monkeys over many preceding years. Of the present lot, eight were kept in the colony at one time, and the remaining ten, during the year following. Every effort was made to keep living conditions standard so that blood sugar changes, fatigue, and the like, which may result from poor care, should not interfere with the investigation. Temperature, light, and air conditioning were standard in the room, as was the diet.[5] The animals were all in good health and had been kept in the colony at least two months before the investigation was started. Average weight was about 3 kilograms. They were seen and handled only by a group of about five people, trained to observe clinical seizures and ordinary cage behavior. All animals were caught for the electroencephalographic recordings at about 8:30 a.m. Two monkeys were removed to the laboratory at one time, as it was found that each subject remained quieter during the recording if another animal was near.

The electroencephalographic procedure was also standardized. The unanesthetized monkey was placed supine in a holding box which restrained him at neck, hips, and chest, but which allowed some movement. Eyes were closed with two thicknesses of gauze bandage to minimize blinking. Needle electrodes were applied in eight positions on the head as shown in the illustrations. This technic is standard for monkeys, and the type of holding box is one used in many laboratories. Bipolar recordings were made on a Grass eight-channel electroencephalograph machine. Frequency analysis of the electroencephalographic record was made on an Offner frequency analyzer, and stroboscopic stimulation was routinely used, as will be reported in detail in a later paper.

Following electroencephalographic recordings in the normal state, cortical operations were carried out according to a routine sterile procedure. At the first operation either aluminum hydroxide was applied to the right motor arm area, or both frontal poles (areas 9 to 12 of Brodmann) were removed. At the second operation many months later, the reverse procedure was carried out. All animals, following application of aluminum hydroxide, developed clinical left-sided seizures which continued periodically throughout the remainder of their lives. Many, but not all, were seen to have generalized seizures as well. First clinical seizures were seen to appear between the second and ninth weeks following operation.

In these experiments the aluminum hydroxide was applied in the following way. A total of about 0.1 cc. of a gelatinous colloidal preparation of the material was injected through a 28-gauge, ½-inch hypodermic needle and a tuberculin syringe into the grey matter of the cortex at a depth of 2 to 3 mm. The needle was inserted four times, each about 3 to 4 mm. from the last, in a small square in the area of arm and hand innervation of area 4. A drop slowly injected produced a slight bleb at the surface. Subsequently at autopsy, there was never any gross sign of cortical damage or adhesions in this area.

The electroencephalographic recordings were appraised in several ways: they were examined for focal and generalized abnormalities; graphs of the frequency patterns were made; and counts of total paroxysmal electroencephalo-

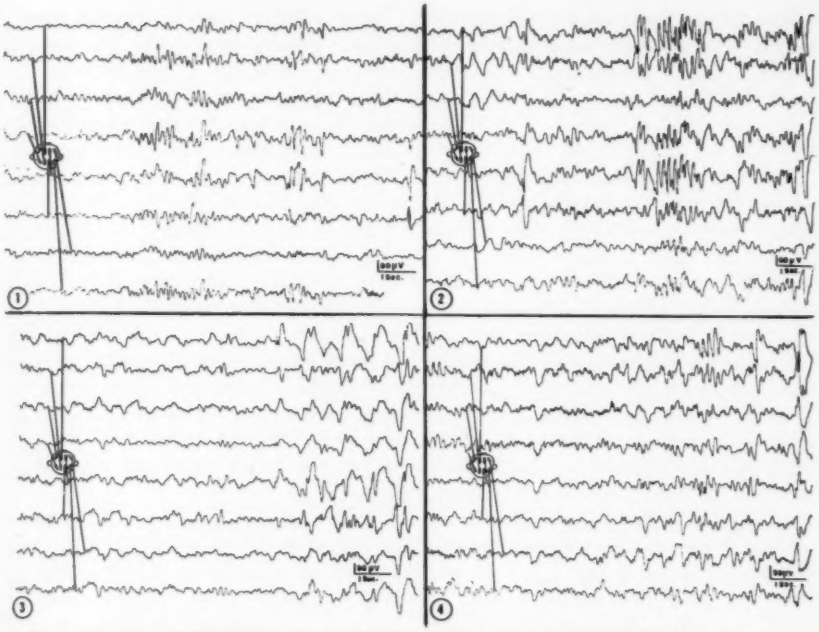

FIG. 1. Electroencephalogram of normal monkey 52, showing paroxysmal generalized activity.
FIG. 2. Electroencephalogram of normal monkey 57, showing bouts of paroxysmal activity most marked bilaterally in frontal regions.
FIG. 3. Electroencephalogram of monkey 52 (see figure 1) following bilateral ablation of frontal poles. Paroxysmal generalized activity most marked in rostral areas.
FIG. 4. Electroencephalogram of monkey 57 following injection of aluminum hydroxide. This monkey had developed focal left-sided seizures before the date of this recording, but was in the quiet and resting state during electroencephalogram period.

graphic activity were carried out. This last was done by examining each page of the resting record which was always made before the stroboscopic stimulation was begun. The total number of pages examined varied between 60 and 100. Any page having paroxysmal activity on it was rated as "paroxysmal," the two other categories being "quiet" when the record was even and of relatively low voltage with the monkey resting quietly, and "artefact" when muscle activity obscured the true electroencephalographic record. The percent of total pages having quiet, paroxysmal, or artefact patterns was then calculated. Eventually it was found that, although there were usually several "artefact" pages to a given record, these could be discounted in the total number.

At least three preoperative normal records were always made, several animals having five or six. The recordings were always made under observation of two workers, one who ran the machines and a second who watched and recorded the monkey's behavior. It was seen early in the investigation that the normal monkeys frequently had rapid, brief twitching movements of fine muscles, fingers,

toes, and face; these were noted and recorded. The observer usually held the monkey's fingers lightly and in this way could feel as well as see the twitches.

RESULTS

1. *Electroencephalographic records of normal monkeys.* In figures 1 to 4 individual electroencephalographic records of four of these monkeys are shown, illustrating the "quiet" and "paroxysmal" phases. It will be seen that in each there is a period of relatively even pattern, followed by a sudden burst of high voltage, irregular, fast and slow activity which is "paroxysmal" in quality. Such paroxysms might last for a few seconds or for several minutes when there would be a sudden return to the low voltage, more regular activity. Figures 1 and 2 are from the records of two normal monkeys. Figures 3 and 4 are records from the same two monkeys each of which has been rendered abnormal by a cortical procedure (in figure 3 by bilateral ablation of frontal poles, and in figure 4 by administration of aluminum hydroxide). The individual patterns before and after operation are indistinguishable in these portions of record.

It was noted while recording that, during the episodes of "paroxysmal" activity the behavior of the monkeys was different from that during the periods of "quiet" pattern. The animals tended to be limp, motionless, and relaxed during the "paroxysmal" periods. These occurred at times when our poorly sound-insulated rooms were relatively silent. A sudden noise or light would produce an instantaneous return to the flatter "quiet" pattern, although there might be no movement of the monkey. Drowsiness or sleep was apparently the situation during the paroxysmal activity.

One further observation was made during drowsy periods of the normal animals: with the hypersynchrony of the electroencephalogram, there very frequently appeared brief, flash-like myoclonic twitchings of the small muscles. These were usually of finger or face, about the mouth. They were usually, but not always, bilaterally simultaneous.

When the amount of paroxysmal activity in each record had been estimated, it was found that there was wide variation between individual animals but that a given monkey tended to have a level of paroxysmal activity which remained throughout all electroencephalographic recordings. These were made at approximately two-week intervals (figures 5 to 8).

This variation in paroxysmal tendency of the normal monkey was consistently related to the degree of sensitivity or responsiveness of the electroencephalogram to any form of stimulus. For example, one constant, although faint, sound was the click of the frequency analyser occurring every ten seconds. In some animals this produced a noticeable sudden change in pattern, probably the result of startle. These were the monkeys having highest per cent of "paroxysmal" activity. Such animals had also the lowest threshold to stroboscopic stimulation and greatest incidence of resultant harmonic wave-forms. Many of them had very poorly regulated alpha activity.

The normal electroencephalograms of *Macaca mulatta* are about as individualistic as are those of human beings. Some have much alpha activity and some very little. The basic alpha rate of the monkey is five to seven per second. There is much less definition of pattern than in man and much less difference

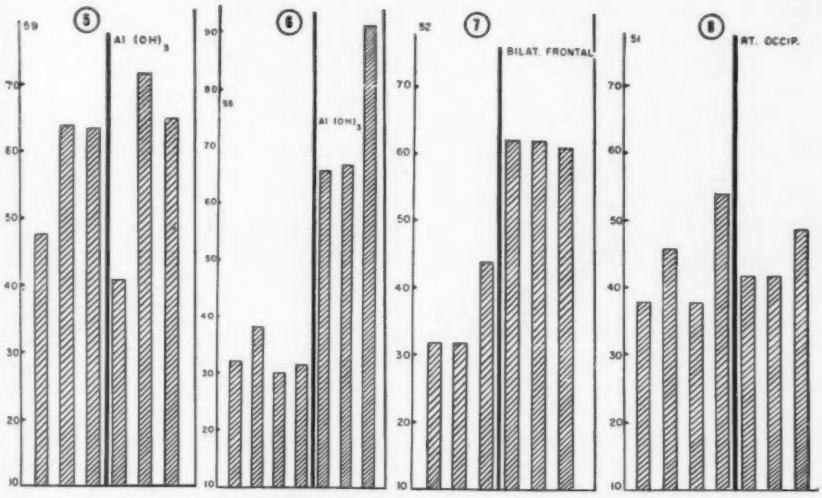

FIG. 5. Percentage of generalized paroxysmal activity before and after injection of aluminum hydroxide.
FIG. 6. Marked increase in generalized paroxysmal activity following injection of aluminum hydroxide into right motor cortex. Columns indicate successive recordings at about biweekly intervals. Ordinates indicate percentage of paroxysmal wave-form.
FIG. 7. Percentage of generalized paroxysmal activity in electroencephalograms taken at biweekly intervals before and after bilateral frontal pole ablation.
FIG. 8. Absence of change in percentage of electroencephalographic paroxysmal activity in control monkey having one occipital pole ablated.

between frontal and occipital poles. These facts are well known and are to be expected, since the cortex of the monkey is relatively less complex and less well differentiated than that of man. For example, ablations of large cortical areas in the monkey will produce almost no focal change, probably because the total recording area is small as well as less well differentiated. Similarly, focal epileptogenic areas are much less well defined in the monkey than in man.

In figure 9 the frequency pattern of four normal monkeys has been traced from the analyzer record. In each instance, eight consecutive frequency tracings from the right frontal lobe have been superimposed. Arrows mark those recordings which, on inspection of the electroencephalographic record, showed "paroxysmal" patterns. High voltage slow and irregular activity appeared in every case. Thus, in *A* the monkey remained awake and the electroencephalogram "quiet" throughout all eight recordings. In *B* the monkey became drowsy and his record "paroxysmal" during two of the eight recorded epochs. In *C* there is only one paroxysmal period, but in *D* there are definitely three and great irregularity in the remaining five epochs.

2. *Metrazol activation.* For a short period during the earlier experiments, Metrazol activation, 0.1 mg. per kg., was used as a means of detecting early changes in cortical excitability following aluminum hydroxide. It was found that the electroencephalograms were always potentiated when Metrazol was given in either the normal or postoperative state.

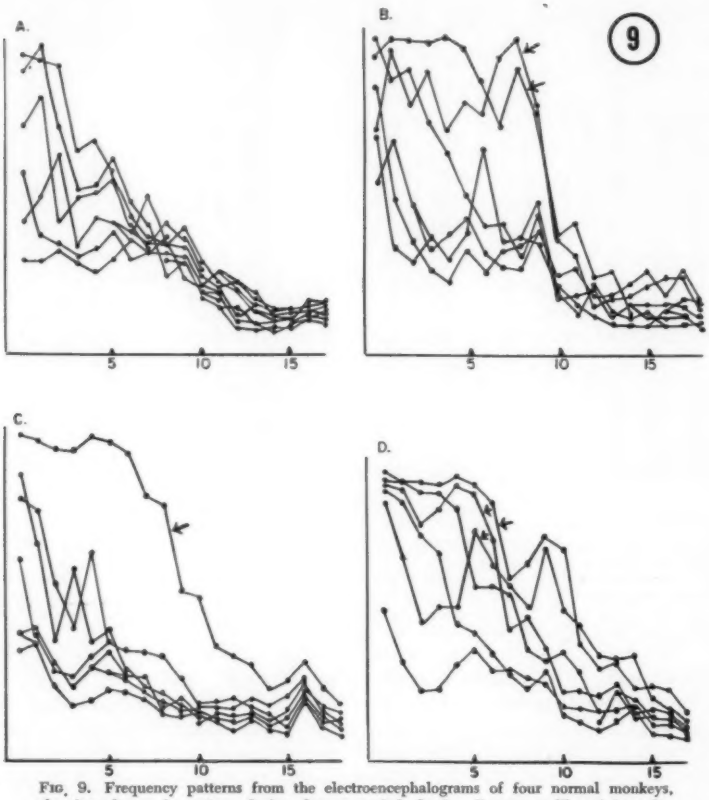

FIG. 9. Frequency patterns from the electroencephalograms of four normal monkeys, showing change in pattern during drowsy periods having "paroxysmal" activity. Ordinates represent height of frequency pips as measured from analyzer record. Abscissae show rates in seconds.

The brief muscle twitching noted in normal resting animals became much more frequent and widespread, "paroxysmal" activity increased, eventually tremor and then true seizures appeared clinically, but it was soon decided that exactly the same changes appeared in the resting quiet animal and that early changes in threshold were as easy to detect in one situation as the other. The use of Metrazol was, therefore, abandoned as unnecessary.

3. *Stroboscopic stimulation.* During the recordings stroboscopic stimulation was routinely applied at the end of the procedure. Flicker frequencies from four to 12 per second were used following a stereotyped procedure. Sensitivity to stroboscopic stimulation, as shown by alterations in electroencephalographic frequency pattern, provided confirmation of the degree of sensitivity and reactivity of the cortex as previously shown by the amount of "paroxysmal" activity

seen in the resting record. As compared to man, it is relatively easy to "drive" the monkey cortex in this manner. Harmonics always appeared and Jacksonian seizures were induced in many of the epileptic animals but in none of the normals or in those having frontal lobe ablations.

4. *The electroencephalograms of epileptic monkeys.* The paroxysmal episodes in the normal monkeys, as described above, were always bilateral and showed no localization beyond the fact that the irregularities and spikes were more pronounced in frontal than in occipital poles. This was also true in the monkeys made epileptic by aluminum hydroxide, except during one early phase of the development of their clinical seizures when there was always a focus of abnormal activity at the site of injection of the aluminum substance. Later, as the symptoms spread, a simultaneous spread of abnormal activity appeared such that paroxysmal wave-forms were always seen bilaterally.

The abnormal activity resulting from the injected substance could usually, but not always, be distinguished from the more generalized "normal" paroxysmal pattern. The focal spikes were sharper and more discrete in many instances. They appeared less frequently in a given record than the generalized activity. The focal activity occurred only in certain records, although the generalized, paroxysmal wave-forms appeared almost regularly in amount and were present to some degree in every record.

The focal spike activity, which was certainly the result of the aluminum hydroxide since it was focal to the area of injection and since it was at times accompanied by focal clinical seizures, never occurred at any time except during the periods of generalized "normal" paroxysmal activity. Furthermore, the muscle twitching described above as occurring only during the "normal" paroxysmal activity continued to appear selectively under this condition, but very often in the epileptic animal the twitching would be more frequent and would be contralateral to the focus of injection. Thus it would appear that the hypersynchrony of the resting animal potentiated the focal seizure activity.

The second condition under which clinical seizures appeared most commonly was that of fright. When these monkeys were caught for examination, they very frequently developed an acute clinical seizure. Or, in a quiet and resting colony of monkeys, the entrance of two examiners with the net to catch one monkey apparently precipitated a seizure in one of his neighbors. The potentiation of seizures by Metrazol has the same effect, very possibly from the same factor of hypersynchrony of cortical activity. Interrelationship between "normal" paroxysmal activity and focal seizures was also indicated by the effects of a clinical attack precipitated by fright. Post seizure, as would be expected, there was often a less marked degree of focal cortical abnormality in a relatively exhausted cortex. The generalized "normal" paroxysmal activity under such conditions was also always diminished.

The type of change in paroxysmal activity which followed aluminum hydroxide injection is shown in figures 5 and 6. In figure 5 it will be seen that the incidence of "paroxysmal" activity in the preoperative records of this particular animal was consistently very high, and became only slightly higher following injection of aluminum hydroxide. One other fact is shown in this figure which

occurred in many animals, namely that on the first postoperative recording the incidence of paroxysmal activity had fallen. This first record was run two weeks after operation. At this time the animals, although fully recovered from operation, were slightly less active and energetic than they became later. If anything, they were more quiet during their recordings. The level of paroxysmal acitvity, however, did not parallel this, which was taken as an indication that the paroxysmal wave-forms, although often present during the drowsy state, were an index of some phenomenon of excitability of the total cortex, either resting or awake, and not a sign of sleep alone.

In figure 6, the pre- and postoperative records of another animal are shown. This monkey had, during the preoperative periods, a rather stable electroencephalographic pattern with relatively high alpha incidence and only about 30 per cent of paroxysmal patterns during four recordings. Immediately following application of aluminum hydroxide to the motor cortex, the incidence of paroxysmal activity more than doubled and has remained so for many months. This animal developed clinical seizures during the second week after operation. It has frequent and severe attacks now, one year after operation.

5. *Electroencephalograms after frontal lobectomy.* A second procedure which produced an increased tendency toward clinical epilepsy is that of bilateral ablation of the frontal poles. The frontal poles were removed bilaterally at a primary operation. This resulted in each case in a rise in total paroxysmal activity, such as is shown in figure 7. No monkey, however, has ever had a clinical seizure following this procedure, although muscle twitchings increased during paroxysmal periods. All these animals showed a definite increase in frequency and severity of paroxysmal electroencephalographic activity when aluminum hydroxide was applied at a second operation. All monkeys previously made epileptic, who had frontal poles removed at a second operation, showed an increase in clinical seizures. Status epilepticus requiring barbiturate medication followed in two such cases. Figure 9 shows the incidence of paroxysmal activity in one control monkey in which an occipital pole has been removed. No increase in paroxysmal activity occurred.

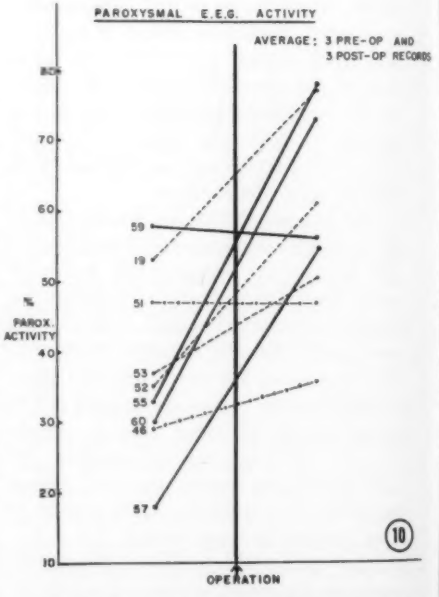

FIG. 10. Percentage of paroxysmal electroencephalographic activity, average of three preoperative and three postoperative recordings. Solid lines indicate those having aluminum hydroxide at operation; dashes, those having bilateral ablations of frontal poles; and dot-dash, two controls.

Figure 10 shows the relative incidence of generalized paroxysmal activity in monkeys having aluminum hydroxide application (55, 57, 59, 60), those having bilateral frontal pole ablations (19, 52, 53), and two controls, one having no operation (46) and the other a unilateral occipital ablation (51). No explanation is obvious as to why paroxysmal activity did not increase in monkey 59 beyond the fact that its initial "normal" paroxysmal activity was the highest in the group. It developed contralateral clinical seizures during the period covered in the graph, as did all other animals of the series. Three later records made on this animal subsequent to the last recording shown in the chart had an average increase in paroxysmal activity to 80 per cent from the 56 per cent shown in figure 10.

6. *Incidence of muscular twitchings.* Perhaps the most interesting finding in this study was that, in every instance during "normal" paroxysmal episodes, there were brief, rapid, muscle twitches of the finer musculature, usually lip, thumb, or fingers, but sometimes toes or wrist. These might be unilateral or bilateral but appeared in many different places in the same animal, although one particular monkey had a propensity for twitching of the right upper lip and several others had one thumb which was apt to be the point "firing" most often. These twitches were never seen during the "quiet" electroencephalographic periods, but always during the first seconds of the "paroxysmal" activity. There were, however, many "paroxysmal" periods for each animal in which no twitching was seen. It was assumed then that twitching might have occurred elsewhere in the musculature and unobserved. Twitches always increased during Metrazol activation. They were also much more frequent when the animals had been made epileptic, and in this latter instance they usually, but not always, appeared in the musculature contralateral to the injection of aluminum hydroxide, the side which eventually developed Jacksonian seizures as the cortex became more excitable.

DISCUSSION

Much of the material presented above is exactly what is to be expected from previous clinical and experimental data. It is felt, however, that the sequence of development of the epileptic seizure and the interrelationships between "normal" hypersynchrony and abnormal epileptic electroencephalographic patterns as seen in these monkeys contribute to our knowledge of the genesis of epileptic seizures in man, and particularly to that of the young child in whom many of the seizure qualities seen in these monkeys are also present.

In the human child, and to a lesser extent in the adult, there is a strong tendency to develop more seizures during strong excitement than at other times. It has been assumed that this is the result of the hypersynchronous pattern of cortical activity which predominates in these two conditions, and this is borne out by our observations on the normal monkeys during drowsy periods and on the animals whose cortices have been rendered abnormal either acutely by Metrazol or chronically by aluminum hydroxide.

The phenomenon of rapid, random muscle twitching in the normal monkey, occurring always in the areas having greatest cortical innervation and only during periods of hypersynchrony, has possibly also an analogy in the human

child in whom myoclonic twitchings are frequent during early sleep. Some epileptic children are said to show these twitches very frequently. They are more frequent in some adults than in others but are never as prevalent as in the child.

It is of interest also that these twitchings became much more frequent in the epileptic monkey or in the animal in whom paroxysmal activity had become more prevalent as the result of frontal ablations. Finally, potentiation of one hemisphere with aluminum hydroxide could shift the site of twitching so that all or almost all, instead of being bilateral, appeared only in the hand opposite the site of injection of epileptogenic substance into the motor hand area.

The fact that there has been a consistent level of paroxysmal activity preoperatively, which has been reasonably constant for each individual monkey, is consistent with the findings in man, as is the fact that once the cortex has been potentiated by operation, the new level of adjustment of paroxysmal activity remains the same although higher. One exception to this occurs when in a postictal period immediately following a clinical seizure, the total paroxysmal activity is temporarily diminished.

The rise in level of paroxysmal electroencephalographic activity which followed bilateral frontal pole ablation seemed remarkably high in every instance and was certainly as great as that seen following the use of aluminum hydroxide. This might have been expected from the fact that clinically in man there is a high percentage of epileptic seizures immediately following frontal lobotomy and occurring in patients not previously clinically epileptic. Since no monkey ever showed clinical seizures after primary ablation of frontal poles, although his twitching became more frequent and his paroxysmal electroencephalographic activity more prolonged, it must be assumed that this operation merely potentiated a cortex previously relatively less excitable. This is borne out by the fact that the same operation in an epileptic monkey always increased the severity and frequency of seizures.

Finally, the observations made here are entirely consistent with the theory first expounded by Lennox[6] that the development of clinical seizures is to a large extent dependent upon the basic paroxysmal tendency of the preepileptic cortex. The character and incidence of postepileptic pattern in these monkeys have been, in every instance, dependent upon those qualities as seen in the preepileptic phase. Such characteristics have endured without alteration from one to three years, which has been the duration of the experiments.

CONCLUSIONS

1. The pattern of epileptic seizures in the macaque monkey has been found to originate in the preepileptic cortical patterning of the individual animal.

2. Paroxysmal, generalized activity appeared in the resting electroencephalographic pattern of all normal monkeys. Its incidence was fairly steadfast for each single animal.

3. No clinical seizures were ever seen in the normal animals, but bilateral, rapid, myoclonic twitches occurred in fingers, toes, and face musculature and were coincident with the hypersynchronous, "normal," paroxysmal activity. These twitches were potentiated by frontal ablation, by Metrazol administration, or when the animals were made epileptic. In the last instance, twitchings never occurred except during hypersynchrony.

4. Total paroxysmal activity either of the "normal" generalized type or of the focal epileptic was always increased by bilateral frontal ablation, but clinical seizures never resulted from this procedure alone.

5. Chronic epileptic seizures produced by aluminum hydroxide applied to motor arm cortex always caused focal clinical seizures which later became generalized. These seizures occurred most frequently during fear or during drowsy periods and, when they appeared during an electroencephalographic recording, always followed a period of generalized hypersynchrony in which spontaneous muscle twitches of the myoclonic variety had been present.

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■ If we inquire into the differences between the various conductors of the five kinds of sensitive impressions that may come from the different parts of the body, leaving aside the four higher senses and the peculiar sensation given by the genital organs, we find that, as regards their excitability, they differ extremely in different parts of their length, and also one from the other. We have shown, nearly six years ago, that the degree of excitability of the conductors of painful impressions varies very much in the different parts of their length: they have no excitability in the central gray matter of the cord, and they have the maximum of excitability in the part of the posterior roots attached to the cord, and the minimum in their passage through the ganglions. But it seems that some of them, ending in bones, in muscles, etc., have no excitability, except in their peripheric extremity; at least, when we press upon the trunk of a nerve in the arm or the leg, we find that there is but very little pain, if any, referred to muscles, bones, and some other parts. It seems probable, therefore, that a number of conductors of painful impressions have no excitability – at least, to a mechanical irritation – in some parts of their length, in nerves.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Neurologic Signs and Symptoms as a Prodrome to Virus Hepatitis

Walter J. Friedlander, M.D.

VIRUS HEPATITIS is an illness caused by at least two different viruses which produce a systemic disease with a particular predilection for the liver. Among the frequent early manifestations before the onset of jaundice are malaise, headache—particularly frontal and retroorbital—myalgia, drowsiness, and back pain. These symptoms are indistinguishable from many other febrile illnesses, and other more specific neurologic signs and symptoms are rare. If jaundice is present at the time the neurologic complications appear, these present no particular diagnostic difficulties. However, Leibowitz and Gorman[1] pointed out that such complications are more frequent before the onset of jaundice than during jaundice, in which case the etiology of the neurologic signs and symptoms may be quite obscure.

We have reviewed 185 consecutive cases of virus hepatitis—infectious hepatitis and homologous serum jaundice; one had clear-cut neurologic signs and symptoms before the onset of jaundice, two had questionable neurologic involvement before jaundice, and two had evidence of neurologic involvement coincident with the onset of jaundice.

REPORT OF CASES

Case 1. (Questionable neurologic involvement). A 45 year old man was admitted to the surgical service on February 24, 1951 complaining of a sudden attack of vertigo on February 12 which was followed by progressive weakness and malaise. On February 14 he became nauseous and noted that his urine was dark and that there was an icteric tinge to his skin. There was no history of exposure to infectious hepatitis, nor had he received any recent parenteral injections.

Case 2. (Questionable neurologic involvement). A 27 year old man was admitted to the medical service on December 17, 1951 with a history of "nervous upset" for two months, which was further characterized by considerable irritability, particularly toward his family, even to the extent of "tearing up furniture." Because of this he had quit his work as a carpenter in order to rest. The patient had noted some decrease in appetite six months previously, and because of this he had received some hypodermic injections from his family physician with good results. About ten days to two weeks before hospitalization, he noted the gradual onset of nausea and anorexia; one week before admission his urine appeared dark, followed three days later by grey stools. During the last few days before admission, he developed slight upper right quadrant pain; jaundice appeared three days before hospitalization. There was no history of exposure to infectious hepatitis.

Case 3. (Definite neurologic involvement). A 60 year old man was admitted to the neurol-

From the neurology section, Veterans Administration Hospital, San Francisco, California.

ogy service on March 23, 1955, having felt unusually tired for a period of three weeks and feverish for one day. On March 18, 1955 he experienced sudden onset of double vision and a severe frontal headache. There was no history of exposure to infectious hepatitis nor recent parenteral injections. On admission to the hospital the general physical examination was normal; the neurologic examination revealed that the deep muscle reflexes were slightly increased on the left as compared to the right, there was an obvious abducens paralysis on the right, and there was a questionable decrease in pain perception over the right side of the face. A lumbar puncture done on March 24, 1955 revealed the following: pressure, 180 mm. of water; trace of globulin; protein, 39 mg. per cent; no cells; sugar, 64 mg. per cent; and colloidal gold curve, 0111110000. An electroencephalogram obtained on March 25, 1955 was interpreted as normal. About 36 hours after admission to the hospital, his sclerae were noted to be slightly icteric and jaundice gradually increased. By April 7, 1955 there were no longer any visual difficulties and the headache disappeared. Agglutination tests for leptospirosis were negative.

Case 4. (Neurologic involvement coincident with jaundice). A 29 year old man was admitted to the neurology service on August 27, 1950 because of generalized aching, fever, urinary urgency, and dysuria for one day. On admission he also complained of anorexia, some headache, and pain on moving his eyes. Four days after admission it was noted that there was a slight icteric tinge to his sclerae. The patient had a stiff neck which was severe enough to warrant a lumbar puncture. The lumbar puncture revealed the following: pressure, 160 mm. of water; three lymphocytes; sugar, 62 mg. per cent; and protein, 31 mg. per cent. Agglutination studies for leptospirosis and heterophile antibody studies were negative. The impression was that the patient was suffering from acute infectious hepatitis rather than a homologous serum reaction, although he had received one parenteral injection on August 15, 1950.

Case 5. (Neurologic involvement probably coincident with jaundice). A 28 year old man was admitted to the medical service on April 9, 1949 with a history of two weeks of malaise, anorexia, vomiting, generalized abdominal cramps, and subsequent jaundice. The patient stated that he had had several somewhat similar episodes dating as far back as 1943, and occasionally during these episodes his stools appeared light but were never clay colored. This particular episode differed from the previous ones in that he subsequently developed jaundice. At the time of admission, neurologic examination revealed absence of all deep muscle reflexes without any other evidence of neurologic involvement; these reflexes were present but hypoactive by May 20, 1949.

DISCUSSION

In 38 reports from the literature[2–39] accounting for 8,167 cases of virus hepatitis or homologous serum jaundice which were reported because of hepatitis and not merely because they had neurologic signs and symptoms, 14 cases had neurologic signs and symptoms before the appearance of the icterus (0.2 per cent). However, this may not be a true index of the prevalence of neurologic disorders, since frequently only the most important signs and symptoms are noted. In our total group, the percentage of neurologic signs and symptoms before jaundice was 1.6 per cent, though in those with definite neurologic signs before jaundice it was only 0.5 per cent.

A total of 31 instances of neurologic signs and symptoms before the onset of jaundice have been culled from the literature.[12,14,20,26,34,37,38,40,42–50] Several reports have been omitted from this group because it was difficult to evaluate the significance of neurologic signs from the history, or the case was not clearly one of infectious hepatitis. Among those excluded were Hiscock's[51] case, where fainting was the first symptom in one of his series of "epidemic jaundice" affecting 69 college students. Among their patients with "occupational hepatitis" Kuh and Ward[52] cited one who developed upset stomach, stiff neck, urticaria,

TABLE 1

36 CASES OF NEUROLOGIC SIGNS AND SYMPTOMS AS A PRODROME TO VIRUS HEPATITIS

Reference	*Area Involved*	*Cerebrospinal Fluid*	*Days Before Onset of Jaundice*	*Type of Virus**
Newman[12]	Encephalitic	—	9	IH
	Neuritic	—	3	IH
Ford[14]	Meningitic	—	4	IH
Findlay[20]	Encephalitic	—	—	HS
Droller[66]	Meningoneuritic	—	—	HS
	"	—	—	HS
	Encephalitic	—	1	HS
Lucke[54]	"	Normal	2	IH
	"	—	—	—
	"	—	—	—
Allen[37]	"	—	72	HS
Bellington[38]	Meningoencephalitic	—	7	IH
	"	pressure normal; 20 cells (90%L); protein 40 mg.%	9	IH
Cockoyne[40]	Meningitic	—	12	IH
Fiessinger[42]	"	—	7	IH
Lemierre[62]	Encephalomyelitic	—	—	IH
Brain[44]	Encephaloneuritic	—	—	—
Schlenker[45]	Meningitic	pressure, protein, cells increased	—	IH
	"	—	—	IH
	"	—	—	IH
Byrne[60]	Meningoneuritic	protein 8 cells (L PMN) increased	2	IH
	"	"	2	IH
	"	"	2	IH
	"	"	2	IH
Weinstein[47]	Meningitic	pressure 165; cells, 90 PML, 24L; protein 26, sugar 81; chloride 122	18	IH
	Meningomyelitic	pressure 100; cells, 2 PMN; protein 79; sugar 21	4	IH
	Meningomyeloneuritic	pressure 190; cells, 2L; protein 20; sugar 100	6	IH
	Meningoneuritic	pressure normal; cells, 2L; protein 32; sugar 92	10	IH
Sterne[48]	Myelitic	—	—	IH
Streifler[49]	Meningoencephalomyelitic	Normal	10	IH
McMath[50]	Meningoencephalitic	"	2	IH
Friedlander	? encephalitic	—	56	HS
	? "	—	2	IH
	Encephalitic	Normal (see text)	6	IH
Friedlander (cases coincident with icterus)	Meningitic	" " "	—	HS
	Neuritic	—	—	IH

*IH=infectious hepatitis SH=homologous serum jaundice

and diarrhea and then three weeks later became jaundiced, but it is not clear whether the initial episode had anything to do with the jaundice. Damodaran and Hartfall[19] stated that 2 per cent of 450 cases of infectious hepatitis among the troops on Malta experienced fainting at the time of onset of illness; it is not clear whether this occurred before or after actual onset of jaundice or whether fainting might not have been associated with severe malaise. Findlay, Martin, and Mitchell[20] reported a case of "blackout" as the initial symptom of homologous serum jaundice, but again the details are insufficient to draw any conclusions. Parker and Adams[53] wrote of a 28 year old man who was admitted because of evidence of heart failure in February, responded fairly well to digi-

talization, and then in March developed paresthesias of the trunk, feet, and hands and became jaundiced two days later. This patient went on to develop profound weakness, mental confusion, peripheral facial paralysis on the right, and flaccid weakness of all extremities and ultimately died. However, the etiology of the disease was not definitely established and it was felt that this was possibly infectious mononucleosis or infectious hepatitis or other disease. Hippocrates[54] described the case of Hermocrates who may have had infectious hepatities: "he developed pain in the head and loins, tension of the hypochondrium – deafness and then on the sixth day, jaundice."

Among the 31 more definite instances of neurologic signs and symptoms, an attempt has been made to group them into encephalitic (including isolated cranial nerve findings), myelitic, neuritic, or meningitic types; several cases had a combination of these. There were 19 instances of meningitic, 14 of encephalitic, nine of neuritic, and five of myelitic involvement. The onset of neurologic signs and symptoms in cases of infectious hepatitis varied from two to 18 days before jaundice appeared, with an average of six days. The time interval between appearance of neurologic signs and symptoms and the onset of jaundice in cases of homologous serum jaundice was noted only in three cases: 72, 56, and one days. Lumbar puncture findings were noted in 14 cases; cerebral spinal fluid was reported as normal in six, the pressure was elevated in one, protein was increased in six, and there was an increase of cells in seven. Details of the increase in pressure and protein were insufficient in the reports commented upon. In all cases that commented, spinal fluid sugar was normal.

In general, the prognosis of neurologic signs and symptoms is good even though the patient may be profoundly ill. Streifler and Feldman[49] reported a 19 year old boy who developed left hemiplegia, urinary retention, and stiff neck, with good recovery occurring before jaundice appeared. Bellington's[38] case 5 was a 26 year old man who was admitted in coma, having athetoid movements, unilateral facial paralysis, stiff neck, and urinary retention; however, these decreased significantly within three days and it was another three days before icterus appeared. Brain's[44] patient developed unilateral convulsions and hemiplegia with mild polyneuritic signs but recovered completely. However, incomplete recovery of neurologic signs and symptoms has been reported, too. One of Byrn and Taylor's[46] patients exhibited spasticity and sensory deficit three months after the neurologic and hepatic signs and symptoms first began. Droller[26] reported a case admitted in "pre-coma" that developed jaundice the following day and subsequently died; the etiology here was probably homologous serum jaundice.

Some cases of neurologic involvement with hepatitis may be simply the coincidence of two diseases occurring at the same time. Cameron[55] cited two cases with meningitis associated with jaundice and suggested that these were probably cerebral spinal meningitis in which intercurrent infectious hepatitis developed. Sterne[48] attempted to relate several cases of apparent infectious hepatitis to acute poliomyelitis because he was able to identify poliomyelitis virus in the stools of these individuals; however, the time sequence was such as to make this conclusion doubtful. In Wein-

stein and Davidson's[47] four patients, acute poliomyelitis was considered a likely diagnosis before jaundice appeared; indeed, the cases occurred during a year when poliomyelitis was prevalent in their locality and this possibility cannot be entirely ruled out. Stokes, Owen, and Holmes[56] reported an outbreak of "peripheral neuritis" in Arakan which coincided with the development of jaundice; however, they felt that the relationship was purely a casual one.

The differential diagnosis of neurologic disease before jaundice appears may be quite difficult. Most patients have the usual systemic symptoms of the pre-ictal stage, including malaise, headache, fever, and myalgia which are indistinguishable from other febrile diseases. The presence of an epidemic of jaundice or exposure to another patient with jaundice may be a useful clue; the usual long incubation period in homologous serum jaundice makes the significance of a history of injections, whether for administration of a drug or infusion or for withdrawal of blood samples, difficult to evaluate since this is now such a common procedure. Hepatomegaly and liver function tests may be important. The appearance of abdominal pain, which is quite common in viral hepatitis, plus neurologic signs, particularly neuritic signs, might suggest porphyria. Poliomyelitis has been considered in quite a few of the patients listed here; fever, myalgia, neuritic and/or meningitic signs, and even pleocytosis in the cerebral spinal fluid could obviously lead to such an impression, and indeed it is quite possible that some of these patients did have poliomyelitis, plus viral hepatitis. Infectious mononucleosis, which is caused by a virus that may be closely related to the viruses that cause hepatitis, may produce a quite similar clinical syndrome.

SUMMARY

1. Even though some reported cases of neurologic signs and symptoms as a prodrome to virus hepatitis might be the coincident occurrence of two separate diseases, it seems reasonable to assume that on rare occasions signs of neurologic involvement may occur in the pre-icteric stage of virus hepatitis

2. Any and all parts of the nervous system might be involved, although meningitic and encephalitic involvement are the most common.

3. The average time between the onset of neurologic signs and the appearance of icterus averages six days in cases of infectious hepatitis, but may be considerably longer in cases of homologous serum jaundice.

4. The spinal fluid may be normal or may demonstrate an elevation of protein, pressure, and a mild pleocytosis.

5. Prognosis and differential diagnosis are discussed.

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SYMPOSIUM OF INQUIRY

Cerebrovascular Disease

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Irvine H. Page, M.D. *Adolph Sahs, M.D.*

Moderator — *Augustus S. Rose, M.D.*

DR. ROSE: This symposium is a new venture; it is designed to be provocative and stimulating. We have brought together a group of individuals who will discuss the subject of cerebrovascular disease with special reference to areas in which there is inadequate information. As you judge, this is a group of experts, and although they will be asked to talk about what they don't know, I assure you that they were selected because of what they do know. We look to them to stimulate our interest in research in this important field of medicine.

As a springboard for discussion, I present the following case summary as an example of the problems and unanswered questions in clinical approach to cerebrovascular disease.

CASE HISTORY

Mr. W. L., age 43, now a patient in a Veterans Hospital in Los Angeles, has been under observation for five months. He received a medical discharge from the Army in 1944, following removal of spleen and shell fragments. Four months previous to hospitalization, he consulted another clinic because of dizzy spells and increasing nervousness. He was found to have hypertension, and reserpine was prescribed. He was followed by that clinic at weekly intervals and a decrease in blood pressure was alleged. However, he lost pep and strength. After one month of treatment he awoke during the night and, while on the way to the toilet, fell to the floor, with weakness and numbness of the left arm and leg. There was no loss of consciousness. After a few moments the numbness and weakness improved, and he returned to bed and to sleep. The next morning weakness of the limbs was still present, but disappeared by the time he arrived at the other clinic for examination. Reserpine was discontinued. During the following two weeks, numbness and weakness of the left arm and leg returned several times, lasting as long as one to two hours. The patient became increasingly anxious and apprehensive.

Six weeks after the first episode, a spell with weakness of greater severity occurred. On admission to Veterans Hospital, a left hemiparesis was found. The patient was tense and anxious. The temporal vessels were prominent. The blood pressure was 260/130. Roentgenograms of the heart showed slight enlargement of the left ventricle. The carotid pulsations were equal and normal. There was awkwardness and weakness of the left limbs, without involvement of the face. There was no objective sensory loss. The reflexes were depressed on the left side, but there was an abnormal plantar reflex. These abnormal signs disappeared after several hours. During the ensuing weeks he had several similar episodes, between which there were no neurologic abnormalities. The electroencephalogram, skull films, and spinal fluid studies were all normal. An arteriogram was not made.

All symptoms and signs have cleared and the blood pressure has gradually fallen. How-

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ever, it has been observed repeatedly that the blood pressure becomes greatly elevated when the patient is apprehensive. Recently his condition has stabilized. He is less anxious and the blood pressure, though slightly above average, remains essentially constant. He has had no spell in two months. There are no residual neurologic findings.

DR. ROSE: As you will immediately see, this case, which is not an unusual type, raises many possibilities for speculation and differential diagnosis.

The first discussion will be by Dr. Millikan.

DR. CLARK MILLIKAN: One of the first things that this protocol brings to mind is the question—What do we know about the ability to anticipate a stroke? Is it possible to learn more concerning this subject, and what advantage will it be if we do learn more about it? I think things are beginning to change a bit in the general field of strokes. Up until a few years ago, the attitude was quite fatalistic as far as treatment was concerned. Now many things are being tried, and in certain areas progress has appeared. One of the important factors is the ability to anticipate the oncoming cerebral or brainstem infarction. How can this be accomplished? The use of new methods of therapy, including anticoagulants and surgery in certain instances, makes it mandatory that we begin to sharpen our wits to try to find out a way to anticipate what is coming in certain categories of cerebrovascular disease. This patient's history is important in that regard. Something that seems much more important now than it did five years ago is the differential diagnosis between cerebral infarction and intracerebral hemorrhage. How can we distinguish more acutely and accurately between these two entities? This is of paramount importance at present. A number of years ago, Dr. Page listed the premonitory symptoms of intracerebral hemorrhage. Little else has been done. Surgeons are approaching the subject of intracerebral hemorrhage more vigorously, and within the last year we have had seven patients with intracerebral hematoma operated on without a fatality and with rather marked improvement in most instances. The use, or the potential use, of anticoagulant drugs in therapy of infarction hinges on this ability to distinguish between infarction and intracerebral hemorrhage. Are there elements in the histories of such patients which will enable us to identify these two clinical entities? Also, is there any way to distinguish clinically a hemorrhagic infarction from a nonhemorrhagic infarction? In which cases can anticoagulants be used safely?

What is the pathogenesis of these intermittent episodes of weakening and numbness that we hear about so frequently? In certain instances, are they produced or initiated by a fall in blood pressure? Perhaps Dr. Page will have some comment to make concerning his experiences with the use of antihypertensive drugs and the incidence of episodes of actual cerebral infarction in patients receiving such drugs. In certain instances, a fall in blood pressure can selectively decrease blood flow to a given area of brain. This is done experimentally, and inferentially it is present clinically. Some believe that vasospasm is the mechanism of genesis of such episodes. Perhaps Dr. Kety will comment on the anatomy and physiology of angiospasm in the brain and its relationship to these episodes. Some investigators believe that minute fragmentary emboli are cast off into the circulation and may produce transient occlusion or par-

tial occlusion of a vessel, then pass on further and leave no important trace behind them. The relationship of internal carotid artery disease and disease within the vascular artery system to such current episodes has also been raised. So one of the principal questions is — What is the pathogenesis of episodes such as this patient suffered?

What is the treatment of the more important of the various categories of cerebral vascular disease? This is an area where great opportunity lies. It would appear that some new ideas concerning categories of cerebrovascular disease need to be included in the old differential categories of thrombosis-hemorrhage-embolism, because other factors are important now in prognosis and in therapy. Two of these factors immediately come to mind. The first is the speed of onset of the catastrophic vascular occlusions. How quickly they come and how rapidly hemiplegia develops seem to be directly related to prognosis. I am a bit pessimistic about the possibility of restoring a massively infarcted area of brain to function. Such massive infarctions most commonly are the result of rapid occlusion. So perhaps some place in the category is needed for time — time of development of the vascular occlusive episode. The second is the site of the lesions. This ties in definitely with treatment, because patients who have intermittent insufficiency of the carotid or basilar artery and thrombosis within the basilar system seem to do very well on anticoagulant therapy. It is no longer sufficient to say that a patient has had cerebral infarction, or embolus in the older sense of the word.

Now I will say a little more regarding treatment. The use of carbon dioxide, nicotinic acid, intra-arterial Papaverine, intravenous Papaverine, stellate ganglion block, and anticoagulants needs further study.

I have asked a number of questions which, at least to me, are unanswerable. From the standpoint of clinical neurology and clinical medicine, programs of study should be initiated which would possibly answer some of these questions by selecting careful data concerning methods of onset, historic elements in the early course of events, accurate information concerning physical examination, and then what happens in terms of recurrence or further episodes. It seems to me that many of these important questions can be answered by such technics.

MODERATOR: Dr. Kety, Dr. Millikan has raised a number of questions, among them the efficiency of the vascular system to carry out its function.

DR. SEYMOUR S. KETY: I would like to talk briefly about the control of the cerebral circulation, because that is the subject about which we know some things and about which we don't know many others, and because basic information on the control of the cerebral circulation is of fundamental importance in understanding cerebrovascular disease.

Now we do know a few things and I think what we know can be put in the form of an equation:

$$\text{CBF} = \frac{\text{ABP} - \text{VBP}\ \text{(pushes blood through the brain)}}{\text{CVR}\ \text{(impedes the flow of blood through the brain)}}$$

We know that the cerebral blood flow is determined by the arterial blood pressure minus the venous pressure at head level, divided by a whole group of factors which we can group as cerebrovascular resistance.

We know something about the blood pressure and its effect on cerebral circu-

lation. As long as the blood pressure is maintained above a certain minimum level, the control of the cerebral circulation lies intrinsically in the local factors which regulate it. We know also that this minimum level is about 70 mm. of mercury, and as long as the blood pressure is kept above this level, the control of the cerebral circulation does not reside in the blood pressure but in the ability of the brain to turn on or off certain faucets which it has. We also know that when the pressure falls below 70 mm. of mercury, there is a progressive embarrassment of the cerebral circulation. What are the factors that can be included in cerebrovascular resistance? Intracranial pressure plays some role in determining the resistance to the flow of blood through the brain, and viscosity of the blood is an important factor, but only where the viscosity is markedly changed in such diseases as anemia or polycythemia. Under normal circumstances viscosity plays little role. We would expect that certain organic changes in the vessels might change the resistance to the flow of blood through them. Sclerosis and thrombosis of certain vessels would also make it more difficult for blood to get through.

Then we have a group of factors which we can group under the heading of neurogenic control of cerebrovascular resistance. Here is the great unknown. We know that there are certain nerves which course along the blood vessels of the brain. These are autonomic nerves and they take their origin from the carotid plexus. They are supplied by the sympathetic chain in the neck and by the parasympathetic fibers which emerge with the facial nerve and continue along with the greater superficial petrosal. What we don't know is why those nerves are up there, because in man, at least, we have no evidence that they do anything at all. We have some evidence that bilateral stellate ganglion block does not cause an increase in blood flow to the brain, and therefore this evidence would suggest that there is not a tonic sympathetic control of the cerebral vessels. Yet, these autonomic fibers are there; they must have a role, and this role has not been explained, certainly not in man. We also know that there are certain chemical controls of the cerebral vessels. Carbon dioxide dilates vessels of the brain and high oxygen tension causes a moderate constriction of these vessels. We don't know, however, how carbon dioxide dilates vessels, whether by some chemical effect on the vessels themselves or by some axon or other intrinsic reflex. This is an interesting and important question. We know what certain drugs do to cerebrovascular resistance, but there are a whole group of drugs whose effect we do not know. We also suspect that certain humoral agents may play a role in the cerebral vessels, but what these humoral agents are and in what diseases they operate we do not know. I hope that Dr. Page will tell us something about serotonin, what these substances may do to cerebral vessels, and what role they may play in certain of these diseases.

Now let us pass from the control of the cerebral circulation to the one crucial question which this case raises: How can we explain the transitory manifestation of a decreased circulation? In the first place, we might consider that some of these cases can be explained on the basis of thrombosis, with the eventual establishment of collateral circulation and the amelioration of the symptoms. I hope that subsequent speakers, who

know much more about this area, may take up this question. How about those cases which show transient paralyses and in which no thrombosis can be demonstrated at autopsy. How does one try to explain this particular phenomenon? As you know, there are at least two theories which have been proposed. The first of these is the theory of cerebrovascular spasm; here we have a great deal of speculation, because this remains only a theory in man. In certain animal experiments, largely as a result of artificial embolism, workers in France and in Sweden have demonstrated a local spasm of cerebral vessels. The only studies that have been done on man to suggest that this may occur are those of Ecker in human cerebral angioradiography, where, at least to the satisfaction of some people, a spasm of cerebral vessels has been demonstrated occasionally. It is only fair to say, however, that this has by no means satisfied everyone; there are alternative explanations for the radiographic evidence which Ecker has obtained. If spasm does occur, how does one ameliorate it? We have no idea about that – and more important, what possible purpose would cerebrovascular spasm have? Usually nature puts things into our organs with a purpose.

In the past, the cardiologists have developed the doctrine of coronary spasm to explain angina and other transient episodes of pain of cardiac origin. I believe it is fair to say that this concept of coronary vascular spasm has given way more recently to a newer concept of coronary insufficiency. No purpose would be served by having the coronary vessels go into spasm, and there is very little evidence that they do. It was found that these phenomena could be explained by an insufficiency of the coronary circulation or a disproportion between demand and coronary blood supply brought about by transitory changes in blood pressure or in cardiac work, without the necessity of invoking a spasm of coronary vessels. I think the same kind of reasoning can be transposed to the brain and one can speak of a cerebral circulatory insufficiency, possibly to take the place of the older concept of cerebrovascular spasm. In cerebrovascular insufficiency we may see the same thing that we see in the heart– a disparity between the supply of blood to certain structures and the demands of these structures for blood. Now what can cause a diminution in the supply of blood to certain structures? Obviously a decrease in the head of pressure which is forcing the blood through them. In this particular case, the patient first noticed his symptoms of hemiparesis as a result of a hypotensive agent. They occurred in the early morning when he had just arisen from bed. We see here all of the factors which might tend to cause a transitory drop in the blood pressure and which could very well explain a transitory disease in cerebral circulation. We know that in hypertension, when the blood pressure falls or when the blood pressure is reduced, the cerebrovascular resistance is also usually reduced. We don't know why this should occur, nor do we know that it always occurs in every individual; therefore, it is perfectly possible that when the blood pressure drops, the cerebrovascular resistance, in certain areas at least, may stay high and thus cause insufficiency. The effect of a cerebrovascular insufficiency and the effects of a decrease in blood flow to the brain would be most manifest in those areas which have the greatest demand for blood. Here we enter into a large

area of ignorance, because, although we know a little about the total circulation through the human brain, we know practically nothing at all about the local circulation – about the circulatory requirements of the various components of the brain. It may be that there was a generalized diminution of the circulation in this particular case, but that only those areas which needed more blood showed the effect. There is considerable work that needs to be done in trying to understand the local circulation of the living brain and how the tone of cerebral vessels somehow adjust themselves to the local metabolic need.

MODERATOR: Thank you, Dr. Kety. Dr. Fisher, the subject of impeding the flow of blood has been raised, and I would like to ask if you would continue the discussion with respect to the specific problem of the blood vessel itself.

DR. C. MILLER FISHER: Several aspects of the case presented can be used to illustrate the difficulties of the pathologist. Where in the brain should one look for a vascular occlusion in such a case? In cortical vessels? In the middle cerebral trunk? In the internal carotid? The anterior choroidal? The basilar artery? The penetrating branches of the posterior cerebral? Lesions in the territory of each of these vessels can lead to combined numbness and weakness. Assuming for the moment that the abnormality lies in the region of the internal capsule, the problem relates to which vessel or vessels supply the internal capsule? If it is agreed that the anterior choroidal or the penetrating branches of the middle cerebral supply the affected region, the next question is – How shall one undertake to look for the obstruction in the vessel? If the lesion in the brain is first examined, the brain becomes cut into so many pieces that the vessels cannot be traced satisfactorily. If the vessels are dissected first, the brain tissue becomes so badly disrupted that the lesion cannot be found, assuming there was one; this illustrates the point that having the brain in one's hands does not always solve the nature of the patient's illness. In attempting an exact pathologic study, the first question to be answered is – Where in the cerebrum or brainstem is a vessel so situated that, if obstructed, there ensue numbness and weakness of the face, arm, and leg? It soon becomes apparent that a detailed knowledge of the vascular supply of the different levels of the sensory and motor systems is badly lacking. I might remind you that Pierre Marie never accepted the neat separation of motor from sensory fibers in the internal capsule; in his opinion the two kinds of fibers were mixed. The arrangement seen in textbooks, in which the motor fibers are separated from the sensory in the capsule, frequently poses a difficulty when the patient has weakness *and* numbness of one side of the body, both the motor and sensory deficit being greater in the arm than in the leg. I suppose we could well investigate the anatomy of the capsule again. The question could be made still more simple – Where in the nervous system can a lesion cause numbness? When a patient is seen with the complaint of numbness, it is very difficult to picture all the possible sites at which the symptom could arise, and yet that information is necessary in adopting rational therapeutic measures as well as in predicting the future course of the illness. Is numbness the reflection of a disturbance to touch, pain, deep sensation, or a combination of these? At what levels of the brain or brainstem can a

lesion give rise to numbness? The failure of ready answers emphasizes the limitations of our knowledge of the fine details of the clinicopathologic correlation of vascular lesions, even in what everyone takes to be an "ordinary straight-forward case."

In many of the commonest pathologic conditions there are problems in pathogenesis and abnormal physiology, and a few of these will now be discussed.

The first is *cerebral hemorrhage*. As far as I know, no one as yet has seen the vessel from which a hemorrhage has arisen. Indeed some pathologists hold that a hemorrhage is a confluence of many smaller diapedetic hemorrhages. Hemorrhage is often attributed to atherosclerosis, but if the site of bleeding has not been seen, then the underlying vascular lesion must surely still be obscure too. The view is widely held that intracerebral hemorrhage is almost uniformly fatal, but this is by no means so, and at routine autopsy an old hemorrhage from which recovery has occurred is seen at least half as often as a fresh fatal hemorrhage. Recently there came to autopsy two cases of small intracerebral hemorrhage, treated in error with anticoagulants, and this recalls the problem to which Dr. Millikan referred – how to distinguish clinically between a small hemorrhage and a thrombosis.

The next subject which deserves a few words is *hypertensive atherosclerotic encephalomalacia*, or so-called "lacunes." These lesions are due to occlusion of the small penetrating vessels going to the deeper parts of the basal ganglia, thalamus, and pons. These small softenings correlate well with the presence of both hypertension and atherosclerosis, and neither is sufficient by itself. The resultant foci of ischemic infarction in the deeper parts of the brain are possibly the most common lesions in all cerebral vascular disease. Atherosclerosis and thrombosis are blamed, but as far as I know no one has methodically examined such lesions and studied the disease process in the vessels leading to the lesions. Many of the strokes which result are preceded by transient warning symptoms, and while the evidence for vasospasm, shifts of blood flow, and progressive thrombosis are heatedly debated, no one has undertaken to investigate carefully the responsible pathologic process.

Next, *hemorrhagic infarction*. Many infarcts are strikingly hemorrhagic for unknown reasons. Most hemorrhagic infarcts are due to cerebral embolism, and while it has been postulated that migration of embolic material may be responsible, proof is still not conclusive. Here is an interesting problem in vascular dynamics which should be capable of solution.

Now, a brief comment on the *collateral anastomotic blood flow*. It is well appreciated that thrombosis of cerebral vessels can occur without symptoms and without brain infarction. I have seen this happen in the case of the vertebral, the basilar, the internal carotid, the middle cerebral, posterior cerebral, and anterior cerebral arteries – complete occlusion and no lesion. When the middle cerebral, posterior cerebral, or anterior cerebral is occluded without infarction, it must mean that sufficient collateral flow is coming to the territory of the affected vessels via the meningeal anastomotic channels. These anastomoses have been studied by Vandereeken and Adams, and the larger connections have been demonstrated. Recently, in re-studying these anastomoses with the dissecting microscope, it has

been found that there is a veritable network of channels between the contiguous major arteries, and as many as 100 channels connecting middle cerebral with posterior cerebral and anterior cerebral can be counted. The tremendous potential anastomotic flow is illustrated by the case of a 54 year old woman who, while in the final throes of severe rheumatic heart disease, auricular fibrillation, and congestive failure, suddenly developed a left hemiplegia and died three days later. At autopsy the right middle cerebral artery was completely and tightly occluded by an embolus. Nevertheless, the entire cortex on that side was grossly intact. On careful examination after fixation, it was agreed that no lesion could be seen in the entire middle cerebral territory on that side. Yet acute arterial occlusion had occurred due to an embolus. At autopsy Neoprene solution was injected into the anterior cerebral artery and it promptly came around on to the lateral surface of the hemisphere. With the slightest pressure on the syringe the solution flooded over from the anterior into the middle cerebral territory and flowed back almost to the embolus. This was a striking demonstration of the abundance of the anastomotic channels. These numerous meningeal collateral vessels are of great importance in the interpretation of vascular disease, and yet their physiology is as yet unstudied.

The problem of *transient ischemic attacks and vasospasm* can be alluded to only briefly. Here the pathologist's easiest job is to show that in many cases vasospasm need not be invoked as a mechanism at all, by demonstrating a definite, well-recognized pathologic entity as the cause of the attack, for example, a lacune. These small infarcts often cause a transient hemiplegia which clears in a day or so. One often hears this type of stroke attributed to vasospasm when actually thrombosis is probably responsible. Another possible cause of a small transient stroke is cerebral embolism. As the embolus moves along the middle cerebral artery, it may cause a total hemiplegia of sudden onset, and in a few hours or so the neurologic deficit may have cleared. Such an attack often is labeled vasospasm, and the role of small emboli is not appreciated. I am sure you know all of this.

At autopsy, sometimes, a large softening is found without any associated vascular obstruction, and again vasospasm is suggested as the mechanism. It is known, however, that embolic material can break up and disintegrate so that it will not be found in the appropriate location at autopsy; another common cause for brain infarction without obvious occlusion is thrombosis of the internal carotid artery in the neck. The postmortem examination must be most thorough before vasospasm is invoked as a mechanism.

A real task for the pathologist comes when he is called on to explain not one single transient episode but repeated ones. These attacks are usually associated with cerebral thrombosis, but the mechanism by which they arise is still obscure and the pathologist has not contributed fruitfully to this problem as yet. Most patients with transient ischemic attacks due to disease in the middle cerebral or penetrating vessels survive, and there is little chance to do a postmortem examination during the acute phase. In disease of the basilar system, the patient often dies and the vessels are seen within a week or two of the time at which transient attacks had been occur-

ring. However, it is an almost hopeless undertaking to examine a mixture of fibrin, platelets, red cells, and fibroblasts stretching from the vertebral to the posterior cerebral, and draw any useful conclusion as to the pathogenesis of the transient attacks. It is desirable to examine cases in which transient attacks had been occurring and in which death occurred from some other cause, such as myocardial infarction. This would provide an opportunity of studying the vascular process uncomplicated by added thrombosis. Then the anatomic substrate for transient ischemic attacks might be better understood. These are only a few of the many unsolved problems in the clinicopathologic study of cerebral vascular disease. There are many others, including Buerger's disease, Binswanger's subcortical encephalopathy, hypertensive encephalopathy, brain swelling, and so on, but time does not allow further discussion.

MODERATOR: Dr. Page, will you continue?

DR. IRVINE H. PAGE: The first problem I would like to take up is the one of the modern treatment of hypertension and the fact that it doesnt seem to do quite what we hoped it would. As you know, there has been considerable success in the management of hypertension, particularly malignant hypertension, and it comes somewhat as a surprise to find that, even though we keep the patient's blood pressure strictly normal, they still go ahead and die of a stroke. So the problem of arteriosclerosis and the problem of stroke are still very cogent ones as far as hypertension is concerned.

Dr. Kety has asked three or four questions that are difficult to answer.

The first question is whether hypotension causes any trouble. I should say the surprising thing is that hypotension causes so little trouble. The old Cohnheim doctrine that you must never lower elevated blood pressure was a thesis that held back proper thinking about the treatment of hypertension more than anything I know. It was his notion that the blood pressure was elevated for a purpose and, if lowered, there would be reduced blood flow to the kidney and resultant uremia. Experiment has shown, however, that the blood pressure can be lowered without producing uremia or strokes. In fact, patients with hypertension usually are very much better off as a result of lowering the blood pressure.

The problem of "little strokes" I will pass over and defer to Dr. Fisher. There are surely lacunae in the brain, both ours and the patient's, I dare say. The problem of encephalopathy is different and I think the mechanism is often spasm. True, the evidence isn't too convincing. Dr. Byron has shown spasm to be presented beyond doubt in cerebral vessels of rats with experimental renal hypertension. Spasm in these cerebral vessels is pretty good evidence that, at least during hypertensive encephalopathy, spasm does occur in renal hypertensive rats. Full-blown encephalopathy in hypertensive patients begins, as you know, with headache, restlessness, somnolence, and finally coma. If an infusion of sodium nitroprusside is given, the blood pressure lowers and the patients come out of coma; if the blood pressure rises again, they go back into coma. You can, to a considerable degree, control the effects of encephalopathy. I think the point should be quite clear that there are different types of attacks from those described which almost certainly are due to small thrombi.

The question of arteriosclerosis is

man's greatest medical problem. We can agree that atheromatosis is civilized man's greatest killer. Knowledge of its nature is primitive. It can be reproduced with uncertain fidelity in most animals. Women are less subject to it than men, and hyperlipemia, hypertension, aging, heredity, and anatomy of the arteries predispose. In countries on a high caloric, high lipid diet, mainly England, United States, Denmark, Sweden, and Holland, there is a high incidence. No method of antemortem diagnosis is available.

If one thinks of the blood vessels as a water filtration system and thinks of the blood pressure as the pressure of filtration in the blood vessels, there is a large amount of filtration going through them all the time. The lipids, or fats, are the only insoluble substances that the body encounters and it has to solubilize them. These fatty particles constantly traverse the blood vessel wall under the pressure of the blood pressure, and the surprising thing to me is that more of them don't get stopped, rather than so few of them. Now why do some of them get stuck? In the effort to keep the lipids soluble, the body forms so-called lipoproteins. The beta lipoproteins are of especial interest simply because they are more unstable – more heavily laden with lipid. Again, man's blood contains more lipid than does woman's. These large molecular aggregates get stuck in the blood vessel wall, they lose their protein, they break down, and the fatty material acts as a foreign substance. It is the tissue reaction to that which constitutes atherosclerosis. There are, of course, other viruses.

Therefore, the pathogenesis of atherosclerosis can be summarized in that the anatomy, biochemistry, physiology of the blood vessel wall, all hereditarily conditioned; the composition of the plasma, lateral arterial pressure, and rate of filtration; the responsiveness of the intimal tissues to filtered products, normal or abnormal; the metabolic capacity of the vessel wall (and I'd like to remind you that the blood vessel wall, like many organs, can synthesize cholesterol) and change in the filtration capacity of the vessel wall all may result from age, hypertensive disease, and metabolic disorder. Because of its multifaceted nature, atherosclerosis is a problem in which you must take into consideration all of the factors in order to arrive at the clinical picture.

I won't go into the question of diet in atherosclerosis. It is one of the most important ones at the present time for the simple reason that the question has been often asked as to whether the American public is eating itself into coronary and cerebral disease. The final answer to this question is not available.

MODERATOR: We will now present the questions submitted by the audience. Each question will be directed to one member of the panel, but all may comment. The first is to Dr. Page: Would you comment on the value of stellate ganglion block?

DR. PAGE: I do not think it is of much value.

DR. KETY: In regard to stellate block, I would like to add that in some cases a stellate block produces improvement in the stroke within a short time and even reproduces the beneficial effect again after regression has occurred. Such a series of events controverts much of the evidence against stellate block. It is important to know if any stroke has been improved dramatically by stellate

block. I have studied many strokes treated by stellate block, and have never seen a dramatic improvement – indeed not even a slight improvement during the next half hour. However, I think that those workers who have described spectacular improvemnt make it worth while to look into the matter very carefully before advising against use of the procedure.

DR. MILLIKAN: If one goes to the literature concerning stellate ganglion block, the score right now is 13 to two – 13 reports in favor of its being efficacious and about two indicating that it doesn't materially change the course of events in cerebral infarction.

MODERATOR: Dr. Kety: Can it be assumed that meningeal and intracerebral vessels react similarly in regard to pressure? Another question is: Do you have any evidence about the alteration in local blood flow associated with focal cerebral seizure?

DR. KETY: I don't know how we can say whether the meningeal or the pial vessels react in exactly the same way as the deeper vessels, since, to the best of my knowledge, we know very little about the regional circulation in the brain. I do know that occasionally investigators obtain results on pial vessels with certain drugs which are different from the results which others obtain on the over-all cerebral circulation. But the possibility does exist that the pial vessels are somewhat anomalous and may not really represent the deeper vessels in the brain.

I don't know of any crucial evidence on the relationship between local cerebrovascular spasm, the alterations in local blood flow, and seizures. I do know that Wilder Penfield has described changes in the color of the venous blood from focal areas of epilepsy and that these venous changes have suggested at times a spasm of the vessels or a remarkable dilatation of the vessels. I don't know of any quantitative data on this point.

MODERATOR: Dr. Fisher: How might the problem of thrombus formation in man be better studied, and how might we better study the integrity of the cerebral vessels without thrombi? There is another inquiry having to do with the possible use of injection technics. Would you care to comment on methods that the group here might use individually to study thrombi, thrombus formation, and the patency of vessels?

DR. FISHER: In regard to the formation of thrombus, and this applies all through the body, the mechanism by which thrombosis develops in relation to atherosclerosis is not fully understood. There are several theories. One of the most recent holds that a small hemorrhage occurs in the subintima of the plaque, damages the endothelium, producing a nidus for platelet deposition, and then thrombus forms. The hemorrhage into the plaque is said to be so extensive at times that it obstructs the lumen by virtue of its own bulk. It has been reported that thrombus formation begins proximal to the plaque, at the summit of the plaque, and distal to it. Some workers are of the opinion that narrowing of the lumen by the plaque with resultant slowing of blood flow and eddying are important factors. It is probably fair to say that in the arteries of the brain, heart, and legs there is as yet no clear idea of the manner in which thrombosis is initiated, nor of the possible rates with which it progresses in different cases. Recently, in studying the deposition of platelets on the endo-

thelium of veins, it has been found that platelets settle out along the lines of junction of the endothelial cells, implying a disturbance of the intercellular cement substance. I do not think enough is known about these matters at present to provide any clues to improved therapy for thrombosis. Does a clot propagate distally and proximally? In the basilar system, of course, thrombosis may start in either vertebral vessel and extend upward gradually along the basilar artery to the posterior cerebral. In the posterior cerebral vessel, clot can form at one place and spread proximally to block one penetrating vessel after another. Certainly in the internal carotid, a clot can form distal to an obstruction and extend up into the middle cerebral artery, particularly if the systemic blood pressure falls. One is often asked if clot can be added proximal to an embolic plug – that is, does thrombosis extend proximally and block further side branches? This occurs but is not often significant, judging from postmortem study.

In regard to the injection of materials. They have one serious drawback, namely, that after injection of the substance into the vessels one is unable to see blood clot, atherosclerosis, and so on, distinctly. Also the injection is done blindly, the lesions often being invisible until the brain is sectioned. However, injection must be carried out before cutting the brain. I have been using Neoprene chiefly to outline the distribution of vessels, not their pathology. In finding obstruction, injection technic is not of much value because of the resultant messy state. Injection may also dislodge material, and any blockage must be carefully examined to rule out artefact. Most of the critical examination of the vascular system must be done without injection technics.

MODERATOR: There are a number of questions which have been submitted by the audience. Several are directed to Dr. Millikan. There are a group of questions about prognosis following an acute cerebrovascular collapse, whether there is any way that one can tell from the clinical findings what the final prognosis of that case is going to be.

DR. MILLIKAN: All we know about attempts at prognosis in supratentorial infarction have to do with what we observed in 250 patients not treated with stellate block or with carbon dioxide inhalations or with anticoagulants. Speed of onset of the infarction seems to definitely influence the prognosis. For instance, mortality is double that of slow-forming infarction in a group of patients having hemiplegia occur over a shorter period of time than three hours. Mortality is 13 per cent in patients whose hemiplegia came on after 12 hours or more. Mortality is about 26 per cent in patients having hemiplegia come on early. As far as recovery of function is concerned, about 21 per cent of patients with the slow infarction remain hemiplegic at the end of two weeks' observation. The figure jumps up for the survivors in the group of fast infarction. In other words, one item that may definitely influence prognosis is the speed of occurrence of the infarction.

Now we are very much interested at the present time in prognosis in basilar thrombosis, intermittent basilar insufficiency, and intermittent carotid insufficiency. I agree with Dr. Fisher's comment a few minutes ago concerning the fact that he has seen instances where complete occlusion of the basilar, the internal carotid, or middle cerebral in

individual instances occurred without evidence of infarction. However, in most instances, I think there is infarction.

We are interested in these intermittent insufficiency syndromes because we don't know how many of them should be given anticoagulants. We have been wrong in withholding therapy in three instances that I know of – patients who subsequently developed basilar thrombosis and died.

As far as the prognosis of basilar system thrombosis is concerned, it is ordinarily considered to be serious. Within the last six months, an article occurred in the literature describing a patient who lived with the syndrome, the inference being that the situation was so unusual that the case was worth reporting. I don't know the exact statistics on survival from basilar thrombosis. We know that certain elements of the basilar system do not seem to carry such a high mortality, posterior inferior cerebellar occlusion being an example of this. So here we need further study concerning what happens to patients with various kinds of occlusions, various size infarctions, speed, and so on. It seems to me that this is one of the areas where attack from the clinicians standpoint is definitely feasible.

MODERATOR: There are still a number of questions which were submitted, but the hour is late. We must, therefore, turn to the last part of the symposium. Dr. Sahs will give us a summary and point up where research and study are needed.

DR. ADOLPH SAHS: It seems incredible that we should know so little about such an important subject. It is unnecessary to make elaborate explanations concerning the value of a symposium of this sort. The subject is of growing concern to physicians generally. We neurologists should try to lead the way in the effort to solve this No. 1 problem – that of cerebrovascular disease. Disorders of the intracranial and extracranial circulatory system constitute the most common neurologic diseases and represent the third most common cause of death in the United States. It is my hope that discussions of the type that we have heard tonight will stimulate more research in the field of vascular diseases of the brain. As you have heard, there are many questions that need solution. My job will be to urge more investigation and research, particularly among those of you who are research minded or who have research programs in operation, in an effort to persuade you to attack this subject directly.

Someone should be able to develop a much better nomenclature and terminology than we are now using. For medicolegal purposes, for example, I think the crude term "cerebrovascular accident" certainly might be altered and a much more satisfactory name attached to this important group of diseases.

This problem seems to me to be one in which team work may answer many problems which the individual researcher may not accomplish, and the statement that the chemist, the physiologist, and others working in this field may help us in our problem certainly should be taken seriously.

I think we've taken many things for granted, particularly the anatomy and the circulation of the brain. Someone should go back into some of these basic problems and tell us more about the embryology of the brain, the formation of the circle of Willis, why the cerebral vessels have only one elastic membrane, and why there is a precarious situation at certain bifurcations. The question of

end arteries always presents itself. In spite of the excellent studies by Cobb, Fay, Fisher, and others, the question of end arteries and the collateral circulation in the brain certainly warrants further investigation. Why are the deeper areas of the brain – for example, the capsular and thalamic areas – apparently devoid of anastomoses? Are their circulatory demands greater so that a relative insufficiency develops? Dr. Fisher has touched upon a subject which seems to me to be very important, that of developing some satisfactory and uniform technic for examination of the brain once it is removed. He has presented to you a major problem, that of getting information without destroying the tissue you are seeking to investigate. And I think, for many of us, carefully controlled clinical studies are in order, and I would ask you please not to consider your clinical problem merely that of another stroke. The patient has a very interesting disorder – a very dynamic condition is taking place in his brain – he has a condition about which we should try to seek as much clinical information as possible.

Panel:

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DR. IRVINE H. PAGE . . . *Director of Research,* Cleveland Clinic, Cleveland, Ohio.

DR. ADOLPH SAHS . . . . *Professor of Neurology,* University of Iowa, Iowa City, Iowa.

Moderator:

DR. AUGUSTUS S. ROSE . . *Professor of Medicine (Neurology),* University of California School of Medicine, Los Angeles, California; *Chairman, Research Committee,* American Academy of Neurology.

■ We do not need to say that anaesthesia may be due to alterations of the posterior roots, and to the nerve-fibers of the various sensitive nerves in any part of their length. We do not need, also, to remind our hearers that anaesthesia may be due to diseases of the encephalon, to poisoning by lead, Arsenic, Belladonna, etc. But there is a kind of anaesthesia which is much less known, and about which we must say a few words. This peculiar anaesthesia depends upon a morbid reflex action; it may arise in diseases of all the viscera, and also from irritations upon any sensitive nerve, in any part of its course.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System,* published in 1860.

CASE REPORT

Multilocular Myelomalacia Following Adhesive Arachnoiditis

W. Kramer, M.D.

BOTH SYRINGOMYELIA AND HYDROMYELIA constitute an anatomic diagnosis. Although there exists an extensive literature on the clinical signs of syringomyelia, symptomatology of hydromyelia is not well established.

An attempt to outline the clinical symptomatology of hydromyelia was done by Biemond.[1] He described a man 21 years of age who suffered from incontinence of urine since the age of three. The clinical diagnosis of hydromyelia was made by puncture of the central canal at the mid-dorsal level. A laminectomy of the lumbosacral region was performed, showing a large cyst of the terminal filament. The cyst was totally removed and was examined histologically, confirming the clinical diagnosis.

The following clinical criteria of hydromyelia were outlined by Biemond: 1) a severe lordosis of the vertebral column, 2) a sensory dissociation over a much larger part of the body than in syringomyelia, 3) the tendon reflexes in cases of hydromyelia remain brisk, but in syringomyelia tendon reflexes of the arms are soon abolished, 4) muscular atrophy is lacking, 5) the symptoms develop very early in childhood and become progressive later on in life, and 6) if the enlargement of the central spinal canal extends to the most caudal part of the cord, bladder disturbances may occur.

Nevertheless, many cases of hydromyelia cause no clinical signs, and in others the differential diagnosis with syringomyelia and other cavities of the cord remains difficult. The filling of the cavity with contrast fluid or air may be of some help. This procedure is certainly indicated for the establishment of the extent of the cavity before or during operation.

The case reported here is interesting and puzzling both from clinical and pathologic standpoints.

CASE HISTORY

A 12 year old boy had had a normal birth. His primary development was not retarded. At the age of two years he had been slightly poisoned by carbon monoxide. Six months later he had been admitted to a hospital because of an influenza meningitis and received treatment consisting of oral sulfonamides and intrathecal injections of a new antibiotic "fungicide" synthetized in Holland during the war (Brocapharm). Shortly after hospitalization a disturbance of gait developed which obliged him to ride a tricycle. At the ages of eight and ten

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a myotenotomy of both Achilles tendons had been performed. Within a brief period after the last operation, his bladder function became disturbed and from that time on he had had an incontinence of urine. Two years later the right elbow joint had become painful and swollen. In April 1954 he was admitted to the neurologic department.

The family history was negative. On examination his intelligence proved to be almost normal. The following degenerative signs were found: scoliosis to the right, scapulae alatae, genua valga, hollow feet, and a syndactilia of the second and third toes. The right pupil was much wider than the left one. There were slight trophic disturbances of both hands, but more pronounced was an arthropathy of the right elbow which in a later stage was not painful. Roentgenographic examination of the elbow joint showed calcium deposits in the surrounding tissues. Tendon and periosteum reflexes of both arms were abolished. The temperature sense was slightly disturbed in the right arm and chest, but was so vague that it could not be reproduced schematically. The abdominal reflexes were abolished on the left side and could only be elicited in the middle third on the right. There was a spastic paraplegia, but the sensibility was undisturbed. Electrical examination of the muscles revealed no gross abnormalities. Furthermore a spina bifida occulta of the first sacral vertebra and cervical ribs was found. Radiographic examination of the skull revealed increased convolutional markings. Pneumoencephalography showed an enlargement of the ventricles, being approximately three times the normal size.

Though a clear sensory dissociation was lacking, the diagnosis of syringomyelia or hydromyelia was considered. As there was a total blockage of the cerebrospinal fluid on lumbar puncture, a tumor of the spinal cord was also possible. The fluid contained a normal number of cells, but the total protein content was slightly raised (45 mg. per cent).

As Lipiodol myelography showed a stoppage at C2, a laminectomy of C1 to C4 was performed. The enlarged cervical cord was surrounded by a thickened dura and arachnoid. In the middle of the cord a cyst was punctured which contained bloody fluid. The fluid was withdrawn and replaced by air, after which a roentgenogram was taken. Figure 1 shows the air in the center of the cord, in the supposed enlarged central canal. The cavity was opened by an incision between the dorsal funiculi and the thickened arachnoid was then separated from the cord.

During the following days the patient developed a temperature, and a liquid-filled cyst developed at the site of the operation. Moreover paresis in the legs grew worse. The general condition improved by repeated puncture of the cyst and with antibiotics.

Two weeks after operation, as the patient was being turned on his back, he became unconscious, with opisthotonus and convulsions; this ceased immediately when he was turned on his abdomen. This was interpreted as a sign of herniation of the cerebellar tonsils into the foramen magnum, due to a posterior arachnitis, caused by the operation and the Lipiodol.

First a ventricle drain was applied by an occipital bore hole, and one month after the first operation cerebellar decompression was performed. A severe arachnitis of the great cistern was found. Membranes of adhesion were removed and the foramen of Magendi was enlarged.

Circulation of the cerebrospinal fluid remained disturbed, so that a perforation of the lamina terminalis was taken into consideration. However, two months after the second operation he suddenly developed meningitis, which necessitated ventricle drainage and antibiotics.

A week after this, 170 cc. of cerebrospinal fluid suddenly ran out and the boy became comatose. On account of the concomitant neurologic findings, a right-sided extradural hemorrhage was diagnosed. He died two hours after the incident.

Autopsy was performed at the University Institute of Pathology. On gross examination the following was found: cervical ribs, spina bifida S1, syndactilia of the second and third toes, a right-sided hydroureter and an enlarged pyelum evidently caused by a valve at the entrance of the vessel, an arthropathy of the elbow joint, and pneumonia.

On opening the skull it was seen that the right hemisphere was compressed by an epidural hematoma of about 250 cc. The pia arachnoid was thickened and was less transparent than normal. The brain weighed 1,310 gm. Except for great enlargement of the ventricles, no gross alterations were present.

The spinal cord was removed except for C2 to C3. The intraspinal dura was adherent to the cord. The spinal cord was weakly developed. A transverse section through the cervical cord showed a large cyst in the center which contained yellowish fluid. Transverse sections at other levels showed areas of necrosis with cavity formation.

Microscopic examination. Pieces of various areas of the hemispheres were embedded in celloidin and stained with hematoxylin and eosin, according to the methods of Nissl and Weigert-Pal. The basal ganglia were treated

FIG. 1. Pneumomyelography of a cyst of the cervical cord.

in the same way. Serial slides were made of the pons and medulla oblongata, and one out of every 20 was stained. Slides were made of different parts of the spinal cord and stained with hematoxylin and eosin and cresylviolet, according to the technics of van Gieson, Holzer, and Pal-Weigert.

There was no evidence of disease in the brain, cerebellum, or brainstem, except the signs of an ependymitis which had evidently developed after operation. The ganglion cells of the cortex were diminished in number, while there was a moderate diffuse increase of glial cells. The Virchow-Robin spaces were enlarged, but the vessels themselves showed no alterations.

The main abnormalities were found in the cord and were evenly distributed throughout its whole length.

The dura mater (figure 2) was considerably thickened by a hyperplasia of connective tissue fibers. There were no signs of inflammation and the walls of the blood vessels were normal.

In the pia arachnoid also, an excess of connective tissue was found to be strongly adherent both to the dura and cord. The spinal vessels were normal, except the anterior spinal artery which showed a thickening of the media in the cervical segments. Nowhere could any obliteration of the lumens of vessels be found. Many of the fibers of the dorsal and ventral nerve roots were atrophic. In the lower cervical segments, patches of nervous tissue composed of glial elements were found outside the spinal cord and between connective tissue of the thickened meninges.

The spinal cord was flattened in a ventrodorsal direction. Cysts were found over the entire length. The cervical segments contained one large cyst which was lying in the dorsal half of the cord, mainly in the dorsal grey matter. In the thoracic and lumbar regions, however, two or more cysts were found that seemed not to communicate. The larger cysts were surrounded by a dense net of glial fibers, but smaller cysts lay among spongy degenerated grey cord matter. The lumen of the cysts was lined by glial tissue. Nowhere could a special arrangement of cells be found except over a small strip in a cervical cord segment. Here 20 glial cells were lying close together forming a palisade.

The central canal nowhere participated in the formation of the cyst. On each level it lay ventral to the cyst. In the cervical cord it consisted of a conglomeration of glial cells without any lumen, but in the thoracic and lumbar segments it was a real canal with a relatively large lumen. One got the impression that it communicated with the spongy tissue surrounding the cysts. Whether the cysts themselves communicated with one another was difficult to ascertain because of artificial openings.

As already described, the arachnoidal space was obliterated. Only in the caudal segments of the cervical cord a large central cyst opened to a space at the lateral margin of the cord (figure 2). It is possible that this constituted a communication with the fluid spaces of the brain. The exact cranial limit of the cervical cyst could not be determined, since part of the upper cervical cord remained in the corpse. It was still present at C3, but there were no traces just above the pyramidal crossing.

FIG. 2. Severe thickening of the meninges, with obliteration of the arachmoidal space. Two cysts are seen in the spinal cord.

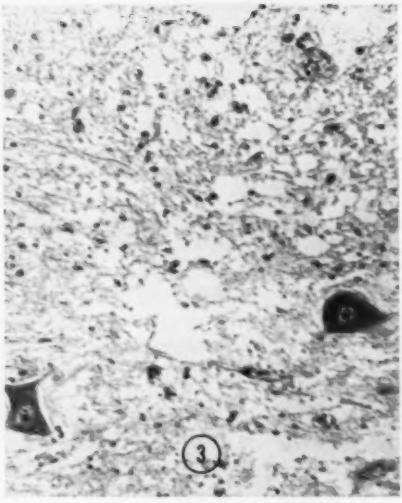

FIG. 3. Status spongiosus of the anterior grey.

Outside the cysts there was little left of the normal spinal cord tissue. The grey substance especially, but also the white, showed areas of cystic degeneration (figure 3). Blood vessels were in excess, leading to a fibrosis by spread of collagen fibers from the adventitia. The walls of the vessels were normal and there was no thrombosis. There was a moderate increase of glial cells which seemed to originate around the central canal. There was no attempt at proliferation or gliosis. Some anterior horn cells were preserved, showing different grades of degeneration. Signs of inflammation were lacking. In the cyst of the cervical cord some compound granular cells containing blood pigment were found.

In the lateral column there was complete destruction of the myelin sheaths and axis cylinders.

The white matter also showed different states of lacunar degeneration. Only in the anterior and dorsal funiculi some myelinated fibers were preserved (figure 4).

SUMMARY OF CLINICAL FINDINGS

A normal, healthy boy who walked easily became ill at the age of two and a half years. He was hospitalized because of a meningo-encephalitis which was treated with oral sulfonamides and by intrathecal administration of an antibiotic synthetized in Holland during the war. Thereafter a disturbance of gait developed, which grew worse during the following years and necessitated orthopedic measures because of contractures. Six years after the primary disease bladder disturbances began, and a year later an arthropathy of the right elbow joint developed. This was very painful in the beginning but became less so later on The clinical course pointed to a process of the cord that developed progressively in a caudal and cranial direction. As this was contradictory to the established diagnosis "diplegia spastica infantilis," the boy was admitted to the neurologic clinic. The right pupil was a little wider than the left. Except for arthropathy of the right elbow joint, the skin of the hands was atrophic and the nails frail. There was no atrophy of muscles and electrical examination showed no abnormalities. The tendon reflexes of both arms were lost. Sensibility was not disturbed except at a later stage. Differences of temperature were poorly localized in the right arm and chest. Muscle power of the legs was poor. There was no atrophy except due to inactivity, and the electric excitability was normal. The left leg was a bit more spastic than the right. Tendon reflexes were increased and the Babinski sign was positive on both sides. Sensibility was unimpaired.

The patient showed various congenital peculiarities, such as syndactily, cervical ribs, and a spina bifida occulta. Moreover,

FIG. 4. Severe degeneration of the fibers of the lateral funiculi. Myelin sheath stain.

a lordosis and scoliosis of the lumbar spine and scapulae alatae were found, which might have been acquired during later life.

Lumbar puncture revealed a complete block in the cerebrospinal fluid circulation, and Lipiodol myelography showed a stoppage at C2. As the convolutional markings of the skull were increased, pneumoencephalography was performed, revealing a severe enlargement of all the ventricles.

Cervical laminectomy showed thickening of the meninges and a large cavity which extended from C2 to C7, as was demonstrated by pneumomyelography.

This was thought to be an enlarged central canal. However, the absence of dissociated sensibility, the arthropathy, and the severe thickening of the meninges with obliteration of the spinal arachnoidal space pleaded against this diagnosis.

SUMMARY OF POSTMORTEM FINDINGS

Postmortem examination showed cystic degeneration of the whole spinal cord, especially the posterior part of the grey matter was altered but cysts also extended into the lateral columns. As far as could be ascertained from serial sections, different cysts seemed not to communicate with one another. Old cysts were bordered by fibrillary glial fibers, but younger ones were situated within necrotic cord tissue. There was a slight dilatation of the central canal at some levels, but at most levels this was not patent. Glial cells were not especially numerous and only a few granular cells were found at the site of operation. The blood vessels were normal, though at some levels the anterior spinal artery showed thickening of its wall. The intraspinal vessels were increased in number in some places and had a thick collar of collagen fibers. No obliteration of the lumen or thrombus could be found anywhere. Signs of inflammation were absent in the entire cord. This was also the case in the meninges, which were thickened by an increase of collagen fibers, leading to obliteration of the subarachnoidal space. Between the roots, outside the cord, there were small pieces of cord tissue and at some levels nervous tissue was found even within a duplicature of the dura.

Except for the enlargement of the ventricles, no abnormalities of the brain were found. There was slight atrophy of neurons of grey matter, while others showed signs of degeneration. An ependymitis was due to secondary infection after the operation.

PATHOGENESIS

The spinal cord lesions were certainly related to the encephalomyelitis during childhood. Influenza bacilli were found in the cerebrospinal fluid. The child underwent lumbar puncture 23 times, during ten of which a fungicide was given intrathecally. He vomited now and then after the injection, and the cerebrospinal fluid became gelatinous and bloody during this treatment.

Six weeks after the onset of illness the boy was transferred from the department of infectious diseases to another hospital because of an umbilical hernia. In neither hospital was paralysis of the legs noted, the only neurologic sign being paresis of the sixth ocular nerve on one side.

Walking was progressively impaired once the boy returned home. This makes it unlikely that a primary myelitis was the cause of paraplegia.

Nevertheless myelitis as the cause of cavity formation has already been accepted by French workers.[2,3] Some Dutch investigators [4,5] have also described a case of "syringomyelia" caused by inflammation. However, in these cases chronic myelitis was supposed.

Acute and subacute necrotic myelitis, such as described by Foix and Alajouanine[6] and by Greenfield and Turner,[7] had other clinical features and pathologic changes.

In 1934 Moersch and Kernohan[8] described three cases of "necrosis of spinal cord" which were accompanied by cavity formation, with no changes in blood vessels. They gained no clear conception as to the

etiologic factors present, but the possibility of a virus disease was considered. However, symptoms developed immediately during a febrile course and the patients died, having been ill for only a few weeks.

The latent period between acute illness and the motor impairment of the legs in this case proves that the cord was not primarily involved. In the author's opinion the lesions described were due to a chronic adhesive arachnitis.

Many clinicians have proved that arachnitis may be accompanied by intramedullary cysts.[9] McLaurin and co-workers[10] produced chronic adhesive arachnitis in dogs by the intracisternal injection of Pantopaque, kaolin, and both agents in the same animal. Slit-like defects were found in the posterior half of the spinal cord, usually in relation to the posterior horns. Four to five weeks after the cisternal injection the central canal was often dilated. The final stage was that of cavitation. The vessels of the subarachnoid space were embedded in the fibrous tissue and appeared to be constricted by it. No special anatomic arrangement seemed to be involved and no consistent pattern was found from animal to animal, except that the cavitations were maximal in the cervical spinal cord, with less frequent involvement of the thoracic portions and none at lower levels. The ependymal cells were preserved in those portions of the spinal cord not involved in the cavity, but ceased abruptly at its margin and were wholly lacking in the cavity itself. The walls of the cavities were covered by necrotic tissue, beneath which lay the attenuated and somewhat fragmented posterior tracts and fibers. About the cavities there was a mild increase in microglia, some of which contained phagocytosed material. Though blood vessels persisted on or near the lining of the cavitations, there was no evidence of hemorrhage or thrombosis.

Chronic adhesive arachnitis is a rare complication of influenza meningitis, and in this case it was probably caused by the intrathecal administration of an antibiotic fungicide.

This assumption is confirmed by a clinician who mentioned the case of a 16 month old boy who was treated with lumbar punctures and oral sulfonamides for influenza meningitis. Three weeks after onset the general condition improved, but there were still 9,000 to 10,000 polynuclear leukocytes in the cerebrospinal fluid. For this reason, 5 cc. of the fungicide was injected intrathecally and repeated on two other occasions during the following days. After this the temperature rose, the child had some convulsions, and the number of leukocytes in the cerebrospinal fluid rose to 18,000. He died six days after the first injection. It was impossible to obtain cerebrospinal fluid by lumbar puncture on the day before death. At postmortem examination the arachnoidal space was filled with a thick coagulated mass. The leptomeninx showed an excess of fibrin with many necrotic leukocytes. The cord itself, however, was not altered and the vessels were normal. This indicates that the spinal cord or its vessels were not primarily involved in this case, but were later affected in the way described by McLaurin and co-workers.[10]

One may consider the possibility of a congenital syringomyelitic cavity existing in the cervical cord prior to meningitis. An argument for this may be sought in a small strip of ependymal cells lining a cavity at this level. In the author's opinion, however, this was caused by stimulation of the division of cells in the neighborhood of the central canal by the tissue alterations. This was facilitated by a dysraphy, as described by Staemmler,[11] as the boy showed other signs of status dysraphicus (cervical ribs, spina bifida occulta). Such a mechanism was also accepted by Schlesinger[12] and Winkler.[4]

The clinical and histopathologic progression may have been due to advancing obliteration of the arachnoidal spaces and by the hydrodynamic alterations within the cord itself. Cerebrospinal fluid penetrating

within the cord tissue loosens first the grey and later also the white matter. This is followed by secondary gliosis and slight fibrosis of the vessel walls. At operation it was found that the pressure in the cavity was high. That spinal cord tissue was under great pressure was also evidenced by herniation of cord substance through a rupture of the pia mater.

The oldest alterations were found in the cervical cord, as in the experimental cases, and cavity formation proceeded in a caudal and cranial direction. Extension of the cavitation in a transverse plane also occurred.

SUMMARY

A 12 year old boy had been treated by intrathecal injections of an antibiotic fungicide at the age of two and a half years because of influenza meningitis. He was entirely cured, but some months later walking became progressively difficult. In the following years a bladder disturbance developed, as well as arthropathy of the right elbow joint, simulating syringomyelia or hydromyelia. There was an internal hydrocephalus and total block in the cerebrospinal fluid circulation on lumbar puncture. Cervical laminectomy revealed thickening of the dura, obliteration of the liquor spaces, and a large cyst. Pneumomyelography showed that the cyst extended from C2 to C8. On histologic examination multiple cysts were found in the entire cord, with signs of myelolysis of grey and white matter. Signs of inflammation were lacking and the blood vessels were normal. It was presumed that the cavities were due to impairment of the circulation of the blood and cerebrospinal fluid by chronic adhesive arachnitis. The intrathecal administration of a rare antibiotic provoked the arachnitis, which in turn caused spinal cord lesions in a predisposed boy with signs of a dysraphic state.

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CASE REPORT

Obstinate Hiccup as a Prodomal Symptom in Thoracic Herpes Zoster

Prompt Cure after Injection of Largactil

P. Efrati, M.D.

THE ASSOCIATION of hiccup and herpes zoster seems to be rare enough to justify presentation of the following case. Textbooks of neurology[1,3,4,8] do not mention this occurrence. Only two reports of such cases have been found.[2,7] Brooks[2] described a case in which herpes zoster, hiccup, and varicella occurred simultaneously. In this case herpes was localized in an area corresponding to the peripheral distribution of the left second and third lumbar roots.

In the case presented here hiccup preceded the appearance of herpes by six days and the skin eruption was localized in the area of the left third to fifth thoracic segments. There was no evidence of infection of the nervous system. The hiccups ceased shortly after a single injection of Largactil.

CASE REPORT

A 44 year old Yugoslavian man was admitted on April 27, 1955. On a previous admission in February 1954 a duodenal ulcer was found and was treated medically. On April 19, 1955 he felt pain in the left anterior chest at the level of the nipple. The pain radiated to the left shoulder and to the back. Two days after the onset of pain he suddenly started to hiccup and continued to do so every few minutes, ceasing only for a while at night. The chest pain continued but there was no fever, nausea, or headache. Home treatment was of no avail and he was sent to the hospital. On the day of his admission a macular eruption appeared in the left thoracic region. The patient had no recent contact with cases of varicella, but a single case had occurred in his family five months previously.

On admission the patient was not able to tell his story because of the obstinate hiccup. He was in excellent general condition. The temperature was normal; there was a maculopapular eruption in the area of distribution of the left third to fifth thoracic nerves. The eruption was most dense in the anterior thoracic region and on the back near the vertebral column. Examination of the abdominal and thoracic organs did not reveal pathologic findings. On neurologic examination no abnormal findings were noted, except for hypesthesia to pinprick, light touch, heat, and cold in the affected area. All reflexes were normal.

Laboratory studies showed an erythrocyte sedimentation rate of 10/26 mm. (Westergreen), hemoglobin concentration of 14 gm. per cent, and a white blood cell count of 8,400 (84 eosinophils, 2,780 lymphocytes, 84 monocytes, and the rest neutrophil granulocytes). Urinalysis was normal. The blood urea concentration was 28 mg. per cent, total cholesterol 241 mg., and blood sugar 81 mg. per cent. Fluoroscopy of the chest was normal.

Immediately after his admission the patient was given ether to inhale for a few seconds and the hiccups ceased suddenly, only to recur an hour and a half later. Further trials with ether were unsuccessful. Spraying of the skin with ethylchloride in both supraclavicular regions near the course of the phrenic nerves

From the department of medicine, Kaplan Hospital for the Negev, Rehovoth, Israel.

failed to relieve the persistent hiccups. However, ten minutes after intramuscular injection of 50 mg. of Largactil the hiccups ceased completely and did not recur for the next four days. On the day following admission the maculopapular eruption progressed to the typical vesicles of herpes zoster. The patient had no pain, but the cutaneous sensory disturbances persisted until the day of discharge from the hospital on May 1, 1955. On follow-up examination June 29 the patient complained of a tickling sensation in the area of the herpes scars, but no objective signs were noted.

DISCUSSION

Hiccup is usually considered to be a pathologic respiratory reflex causing clonic spasm of the diaphragm. Its source may be either peripheral or central.[5] According to several authors, impulses induced by peripheral irritation are conveyed along sensory fibers included in the phrenic and vagus nerves, whereas afferent impulses are discharged through motor phrenic fibers. Central causes may influence the spinal cells of origin of the phrenic nerves or higher centers in the brainstem connected with them. In the case published by Brooks,[2] a central infectious process was assumed to be the cause of the hiccup, whereas the herpes appeared in a remote region. In the present case the irritation causing hiccup apparently originated in the dorsal spinal root ganglia of the left third to fifth thoracic nerves, the area of distribution of the herpes. The efferent part of the reflex arc consisted of the phrenic motor fibers. The possible pathways pursued by the impulses causing the hiccup are:

1. Fasciculus cuneatus, nucleus cuneatus, intercalated reticulospinal fibers, spinal motor cells of the phrenic nerve, diaphragm.
2. Fasciculus cuneatus, gray column at the level of third to fifth cervical segments, motor cells of phrenic nerve (with or without intercalated spinal neurons).
3. Spinothalamic afferent fibers, reticular formation in the medulla oblongata, intercalated reticulospinal fibers, phrenic motor cells.
4. Spinothalamic tract, posterolateral thalamic nuclei, dorsomedial thalamic nucleus (magnocellular portion), hypothalamus, reticular formation of medulla, phrenic nerves.

The last suggestion is based on the assumption that a part of the complex reflex arc reaches the hypothalamic level. It is in the light of the foregoing assumptions that the influence of Largactil may be explained. Hopkin,[6] in reviewing the French literature on the action of chlorpromazine, emphasizes the action of the drug on reticular formation of the brain. Other authors assume a direct action on hypothalamic centers. The striking cessation of hiccupping after the administration of a single injection of Largactil may indicate a blocking action for this drug. Such action would also explain its effectiveness in the treatment of postoperative hiccup.[9]

SUMMARY

A case in which hiccup preceded the appearance of herpes zoster in the left third to fifth thoracic segments is described.

Inhalation of ether and anesthesia of the supraclavicular skin areas with ethylchloride failed to relieve the persistent hiccupping. A single intramuscular injection of 50 mg. of Largactil, however, caused cessation of the hiccup within several minutes. The possible pathways of the impulses involved in hiccupping and the mode of action of Largactil are discussed.

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Neurology

BOOK REVIEWS

Recent Advances in Neurology and Neuropsychiatry

Sir Russell Brain, Bt., D.M. and E. B. Strauss, D.M., D.Sc. ed. 6, 1955. Boston: Little Brown & Co., Publisher, 311 pages. $7.50.

It is now ten years since the appearance of the previous edition of this familiar and extremely useful resume of progress. The volume has never been intended as a systematic digest of current literature, but rather as an exposition in summary form of what the authors regard as the most important and probably permanent contemporary contributions from all of the neurologic sciences to clinical neurology and neuropsychiatry. The decade covered by the present edition has been an exceptionally fruitful one for the accumulation of new facts and the formulation of new concepts, and it can be said that the authors' selection from this immense offering has been a discerning and well-balanced one. The presentation, too, is as clear as it is concise. References to the literature, though not numerous, are for the most part important and definitive ones.

It is heartening to note how largely in the perspective of the book the developments in neurophysiology tie in with advances or potential advances in neuropsychiatry. This is reflected not only in the chapters dealing with the physiology of consciousness, sleep, hallucinations, and prefrontal leukotomy, but also in those concerned with the physiology of the temporal and parietal lobes.

In the area of clinical neurology the most notable chapter is that on "The Intervertebral Disc and Spondylosis." This is a topic to which Sir Russell Brain has himself contributed in an important way, but it is also one deserving of relatively detailed attention in its own right. Other items of particular clinical interest are carcinomatous neuropathy and myopathy, inclusion body encephalitis, the neurologic complications of liver disease, and the treatment of myasthenia gravis by thymectomy. Separate sections in ancillary lines of diagnosis and treatment have been contributed by other authors, one on electroencephalography by Dr. Denis Hill, one on neuroradiology by Dr. David Sutton, and another on intracranial tumors by Mr. Northfield.

The book as a whole will have greatest value for medical students, general practitioners, and others who have had no occasion to follow the neurologic literature of the past ten years. It is, as the authors stated in their preface to the first edition, an "auxiliary text-book of *applied* neurology" and as such it is admirable.

R. B. R.

Medical Research: A Midcentury Survey

Esther Everett Lape, Editor. 1955. Boston: Little, Brown and Company. Vol. 1, 765 pages; vol. 2, 740 pages. $15.

THE AMERICAN FOUNDATION, since its establishment by Edward Bok in 1924, has surveyed the detailed and basic background of many important problems. This present report on research in biology, chemistry, and physics in relation to the maintenance of high standards of medical education and medical care resulted from the conviction that medical research is the base of adequate medical education and care. Medical progress comes through research, and fundamental reesarch at basic levels must precede clinical application.

The first of the two volumes is a general one, but it is a far-reaching study of the background of medical research, especially in the perspective of biologic, chemical, physical, and mathematical sciences. In it are reviewed the current trends and problems in medical and biologic research in the United States. The various agencies which carry on, support, and contribute to research are discussed individually.

The second volume turns from the general to the specific, and nine major baffling subjects are reviewed in detail. The subjects of cancer, fertility, arteriosclerosis, hypertension, tuberculosis, virus diseases, and the rheumatic syndromes are of interest to all medical readers, but the two last chapters, those dealing with alcoholism and the biology of schizophrenia, will be of special interest to the readers of NEUROLOGY. The discussion of research needs and current concepts in schizophrenia is comprehensive, well organized, and adequately balanced. While both psychologic and physiologic factors are fairly assessed, stress is placed on anatomic, physiologic, electrophysiologic, and biochemical mechanisms in mental disease. Current and recent investigations on mental disease are lucidly discussed and analyzed. It is refreshing to learn that even outside the field of neurology there is an increasing trend toward an attempt to understand mental disease on a basis of physiologic and biochemical changes in the nervous system.

R. N. DeJ.

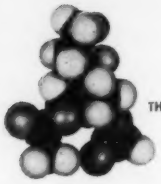
The Blood-Brain Barrier: With Special Regard to the Use of Radioactive Isotopes

Louis Bakay, M.D. 1956. Springfield, Illinois: Charles C Thomas, Publisher. 154 pages. $5.50.

THIS is a well-planned, informative monograph. The history of the development of knowledge of the blood-brain barrier concept from the time of Paul Erlich, followed by a discussion of its histology, embryology, and comparative anatomy, leads the author to his main thesis which is the elucidation of the function of the blood-brain barrier by means of a radioactive phosphorus, P-38. Here, the author records his own basic contributions. It is emphasized that the use of radioactive ions permits the use of rapid and fairly accurate identification of their exchange. In this way, the relatively high permeability of the pineal and pituitary glands, the area postrema, and the tuber cinereum are demonstrated in experimental animals and in man.

The discussion of the studies of local changes in permeability in brain trauma, infections, and cerebral thrombosis puts the basic data into line for clinical application. The concluding chapters on permeability in cerebral neoplasms and on methods of diagnostic utilization bring the work to a close. This book will repay careful reading and the amount of collected classified data makes it a valuable one for reference.

A. B. V.



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AUGUST, 1956

Sixth International Neurological Congress (Brussels - 1957) The Sixth International Neurological Congress will be held in Brussels, Belgium (July 21-28, 1957), in conjunction with the First International Congress of the Neurological Sciences.

Honorary Presidents and the Executive Committee The officers of the Sixth International Neurological Congress comprise the honorary presidents: Sir Gordon Holmes, Dr. Andre-Thomas, and Prof. Georges Guillain; Prof. Th. Alajouanine, Prof. Antonio Flores, Prof. G. H. Monrad-Krohn, Dr. Knud Krabbe, and Prof. Henry Alsop Riley; and members of the executive committee: Prof. P. Divry, honorary president; Prof. Austregesilo, honorary vice-president; Prof. P. van Gehuchten, active president; Dr. R. A. Ley, first vice-president; Dr. Ludo van Bogaert, secretary-general; Dr. J. Radermecker assistant secretary-general; Dr. J. Titeca, treasurer; and Dr. R. A. Ley, editor of the transactions. Also on the executive committee are the vice-presidents chosen as delegates to the congress from many countries throughout the world. Representing the U.S.A. and Canada as vice-presidents are Professors H. Houston Merritt and Wilder Penfield.

First International Congress of Neurological Sciences At a preliminary reunion held in Brussels (Sept. 6-8, 1955), the members of the program executive committee of the Sixth International Neurological Congress convened with the international delegates of several specialized neurologic disciplines, which, though bound by common interests to the central core of neurology, have organized international congresses of their own: neurologic surgery, neuropathology, epilepsy, electroencephalography, and neuroradiology. The result of this preliminary planning session was the affiliation of all of the international congresses of allied neurologic disciplines into a single coordinated international convention. All independent congresses will meet simultaneously in Brussels in 1957 as the First International Congress of the Neurological Sciences. The congresses scheduled to meet in Brussels under the new coordinated program are: Sixth International Neurological Congress; First International Congress of Neurological Surgery; Third International Congress of Neuro-

pathology; Fourth International Congress of Electroencephalography and Clinical Neurophysiology....The broad title of neurological sciences was adopted to allow for participation in future congresses of additional neurologic disciplines, such as neuroanatomy, neurochemistry, neuropharmocology, and so on.

Administrative Structure The general organization and administration of the First International Congress of Neurological Sciences is the responsibility of an executive committee and an administrative bureau. The former is under the chairmanship of the president of the Sixth International Neurological Congress (Prof. P. van Gehuchten), aided by the presidents of the affiliated congresses, who serve as committee vice-presidents. The latter is composed of President van Gehuchten and secretary-general of the neurological congress (Dr. Ludo van Bogaert), assisted by the general and administrative secretaries of the affiliated congresses.

Program Emphasis and Design The multidisciplinary aspects of the First International Congress of Neurological Sciences require a program emphasis and design somewhat different from the traditional programs of previous international neurological congresses. Accordingly, delegates at the preliminary reunion in Brussels adopted a coordinated program organized to highlight two principal topics of common interest to the congress as a whole, and several main topics of individual interest to the particular discipline represented by each affiliated congress (neurology, neurological surgery in association with neuroradiology, neuropathology, epilepsy, electroencephalography and clinical neurophysiology), but which, as far as possible, are pertinent to the interests of the entire congress....Sessions for the presentation of miscellaneous individual communications are arranged for, but are to be restricted in number and will be grouped in appropriate subdivisions....Each affiliated congress will organize its individual program concerned with its own distinct interests.

Principal Topics of Common Interest Prof. Raymond Garcin (Paris) and Sir Geoffrey Jefferson (Great Britain) are to organize and conduct the presentation of the two topics of common interest, to be held Monday and Tuesday (July 22-23). These sessions will be devoted to reports and discussions on extrapyramidal pathology (Garcin), and on the significance and interpretation of modifications of the conscious state (Jefferson).

M. S. is Principal Topic of Neurological Congress Multiple sclerosis is the main topic for sessions of the Sixth International Neurological Congress, under the direction of Prof. H. Houston Merritt, 710 West 168th Street, New York 32, N. Y. Other selected principal topics of interest to

particular congresses are: the pathologic aspects of multiple sclerosis, Congress of Neuropathology (Dr. Armando Ferraro, topic director); supratentorial angiomas and therapeutic applications of hypothermia, Congress of Neurological Surgery in association with the Symposium Neuroradiologicum; and subcortical and temporal lobe epilepsy, International League Against Epilepsy, which will be a follow-up discussion of the First International Colloquium on this subject, held in Marseille in 1954, and a Second Colloquium to be held at the National Institute of Neurological Diseases and Blindness (Bethesda, Md.) in March 1957....All principal topics, whether of common or special interest, will be organized by the topic directors, who will decide upon the number and kind of presentations and the time allocated for presentations and discussions.

Chronology of Scientific Sessions and Other Events Following the original recommendations by Drs. Ludo van Bogaert and J. Radermecker the first day of the congress, Sunday, July 22, will provide for registration of members, an official morning meeting of the International League Against Epilepsy, the plenary opening session of the congress in the afternoon, and a formal reception for participants in the congress in the evening....Monday and Tuesday, July 23 and 24, will be devoted exclusively to a presentation of the two principal topics of common interest to the entire congress. On Wednesday morning, July 25, the main topic of the Neurological Congress will be presented; in the afternoon the main topic of the Neuropathological Congress. The remaining topics of special interest to individual disciplines of the other affiliated congresses are scheduled for Thursday, July 26....Also during the first four days of the meeting, each individual congress will have facilities for special minor topics, grouped communications, and executive sessions....Friday and Saturday (July 26 and 27) will be devoted to miscellaneous communications and minor topics. Sunday, July 28, the last day of the congress, is reserved for individual and joint executive sessions of the various affiliates for the selection of a site for the Second International Congress of Neurological Sciences and to allow for an excursion to Louvain to celebrate the centenary of the birth of Arthur van Gehuchten.

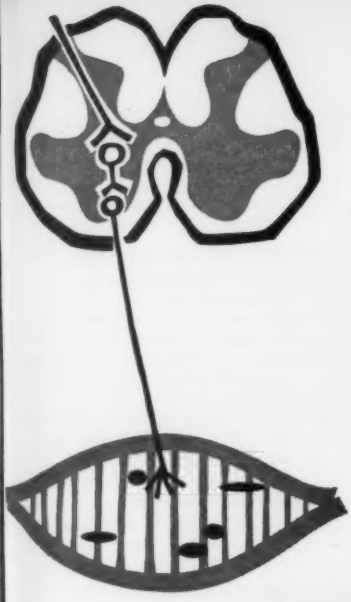
Miscellaneous Communications and Minor Topics The scope and program design adopted for the congress at Brussels makes it necessary that all proposals for the presentation of miscellaneous communications and minor topics before any of the affiliated congresses be passed upon by the national committee of an affiliated congress and obtain final acceptance by the executive committee of the Congress of Neurological Sciences. Each member may present not more than one communication in which his name appears as an

author or co-author. At least one author of each communication must appear in person at the congress to present his communication. Any author failing to present his communication before any session of the congress will not be entitled to participate in future congresses. Titles and summaries (not to exceed 250 words) of communications offered for presentation at the Sixth International Neurological Congress must reach Dr. Pearce Bailey, Secretary of the Committee for the United States, National Institute of Neurological Diseases and Blindness, Bethesda 14, Maryland, before February 1, 1957. No presentation will be placed on the program unless the author has registered as a member of the congress.

Types of Membership, Fees, Procurement of Applications The membership of the congresses shall comprise active, associate, and auxiliary members. Applicants for active membership in the Sixth International Neurological Congress or the Third International Congress of Neuropathology must be members of, or present endorsement by, a national or recognized local neurologic, psychiatric, or neuropathologic society. Physicians and scientists in fields other than those represented by the congresses are eligible for associate membership. Non-medical persons, such as members of families and others interested in the congresses, may register as auxiliary members.... The fee for active members is $15.00; for associate members, $10.00; and for auxiliary members, $5.00....Application forms for membership in the Sixth International Neurological Congress or the Third International Congress of Neuropathology may be obtained from Dr. Pearce Bailey, Secretary of the Committee for the United States, National Institute of Neurological Diseases and Blindness, Bethesda 14, Maryland; for membership in the First International Congress of Neurological Surgery from the secretaries of the several national neurosurgical societies in the U. S.; for membership in the Fourth International Congress of Electroencephalography and Clinical Neurophysiology from Dr. R. G. Bickford, Mayo Clinic, Rochester, Minn.....Appointed as official travel agencies for the congresses are Thomas Cook and Son, Inc. and the American Express Company.

Official Languages and Interpretations Reports and the summaries of communications will be published in French and English. Negotiations are under way for simultaneous earphone interpretations in English, French, and German.... Additional information on publications and translations, as well as on highlights of the congress, will appear in forthcoming issues of the Newsletter as the program develops.

Pearce Bailey



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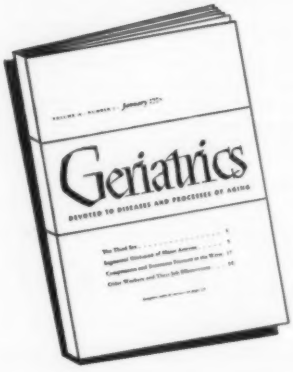

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